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(54) Title: UREA DERIVATIVES AS INHIBITORS OF CCR-3 RECEPTOR

(57) Abstract: Urea and amide derivatives inhibit cell function of the chemokine receptor CCR-3. These compounds offer an effective means for treating a range of diseases thought to be mediated by the CCR-3 receptor. A variety of useful area and amide derivatives can be synthesized using liquid and solid-phase synthesis protocols.

UREA DERIVATIVES AS INHIBITORS OF CCR-3 RECEPTOR

BACKGROUND OF THE INVENTION

The present invention relates to certain urea derivatives that are inhibitors of CCR-3 receptor activity, methods for preparing these compounds, pharmaceutical compositions containing such compounds and methods for their use.

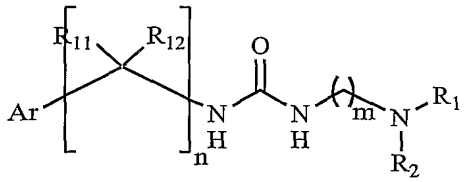
Chemokines are chemotactic cytokines that are produced by a variety of cells to attract leukocytes to sites of inflammation or lymphoid tissue. CCR-3 is a chemokine receptor that is expressed in a variety of cells, including, but not limited to, eosinophils, basophils, T cells and dendritic cells. See Ponath, P.D. *et al.*, *J. Exp. Med.* (1996) 183, 2437-2448; Yamada, H. *et al.*, *Biochem. Biophys. Res. Comm.* (1997) 231, 365-368; Sallusto, F. *et al.*, *Science* (1997) 277, 2005-2007; Sato, K. *et al.*, *Blood* (1999) 93, 34-42. CCR-3 is also known as a co-receptor to HIV virus infection. See He, J. *et al.*, *Nature* (1997) 385, 645-649. Several chemokines including eotaxin, eotaxin-2, RANTES, MCP-2, MCP-3, MCP-4 bind to CCR-3 and activate cell functions such as intracellular Ca^{2+} mobilization, chemotactic response, superoxide anion generation and cell aggregation. See Forssmann, U. *et al.*, *J. Exp. Med.* (1997) 185, 2171-2176; Heath, H. *et al.*, *J. Clin. Invest.* (1997) 99, 178-184; Uguccioni, M. *et al.*, *J. Exp. Med.* (1996) 183, 2379-2384; Tenscher, K. *et al.*, *Blood* (1996) 88, 3195-3199; Sato, K. *et al.*, *Blood* (1999) 93, 34-42. In particular, eotaxin exhibits a potent and specific chemotactic activity for eosinophils via binding to CCR-3, *in vitro* and *in vivo*. See Ponath, P. D. *et al.*, *J. Clin. Invest.* (1996) 97, 604-612.

Tissue eosinophilia is observed in a number of pathological conditions such as asthma, rhinitis, eczema, inflammatory bowel diseases and parasitic infections. See Bousquest, J. *et al.*, *N. Eng. J. Med.* 323, 1033-1039; Middleton, Jr., E. *et al.*, Chapter 42, ALLERGY PRINCIPLES AND PRACTICE (4th ed.), volume 2 (Mosby-Year Book, Inc. 1993). In asthma, the airways of patients are infiltrated by a large numbers of eosinophils, and eotaxin production in bronchial mucosa and bronchoalveolar lavage (BALF) is increased. Several studies have suggested a strong correlation between the number of eosinophils in BALF, the eotaxin level in BALF and the clinical parameters of disease severity. See Walker, C. *et al.*, *J. Allergy Clin. Immunol.* (1991) 88, 935-942; Ying, S. *et al.*, *Eur. J. Immunol.* (1997) 27, 3507-3516. Furthermore, pretreatment with a CCR-3-antibody has been shown to block chemotaxis and Ca^{2+} influx induced by eotaxin, RANTES, MCP-3 or MCP-4, suggesting that most of the eosinophilic response to these chemokines in allergic and eosinophilic patients is mediated through CCR-3. See Heath, H. *et al.*, *J. Clin. Invest.* (1997) 99, 178-184. Similarly, it has recently been disclosed that certain cyclic amine derivatives are antagonistic to CCR-3 and may be useful for treating eosinophil-mediated allergic diseases. See EP 0903349A2. Also, CCR-3 expression on human Th2 type T-cells and human cultured dendritic cells mediates cell functions such as chemotactic response. See Sallusto, F. *et al.*, *Science* (1997) 277, 2005-2007; Sato, K. *et al.*, *Blood* (1999) 93, 34-42. In addition, anti-CCR-3 antibody has been shown to inhibit aggregation of T-cells and dendritic cells, suggesting CCR-3 may regulate the interaction of these cells during the process of antigen presentation. See Sato, K. *et al.*, *Blood* (1999) 93, 34-42. Therefore, CCR-3 inhibitors may also be useful for regulating immune responses.

These examples suggest that CCR-3-mediated diseases may be treated using compounds that inhibit CCR-3 activity. Because CCR-3 is present on many cell types, however, and is responsible for a variety of disease states, an arsenal of compounds that inhibit CCR-3 activity is required to treat CCR-3-mediated diseases effectively.

SUMMARY OF THE INVENTION

To the ends of making available (i) compounds that inhibit CCR-3 receptor activity and (ii) an approach for treating CCR-3-mediated diseases, there is provided, in accordance with one aspect of the present invention, a compound having the following formula, Formula (I).



Formula (I)

or a salt, hydrate, stereoisomer or complex thereof, wherein:

n is 0 or 1;

m is 2, 3, 4, or 5;

R11 and R12 are independently selected from the group consisting of hydrogen, halogen, alkyl, aryl and heteroaryl

wherein the alkyl, aryl or heteroaryl is optionally substituted with one or more groups independently selected from the group of consisting of hydrogen, hydroxy, halogen, trihalomethyl, alkyl, alkoxy, cyano, nitro, amino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, and cyanoguanidino;

Ar is aryl or heteroaryl

optionally substituted with one or more groups independently selected from the group consisting of hydroxy, halogen, trihalomethyl, trihalomethoxy, alkyl, alkoxy, cyano, nitro, amino, carboxy, alkyloxycarbonyl, arylmethyloxycarbonyl,

carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, cyanoguanidino, aryl

optionally substituted with one or more groups independently selected from the group consisting of hydroxy, halogen, trihalomethyl, alkyl, alkoxy, cyano, nitro, amino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, and cyanoguanidino,

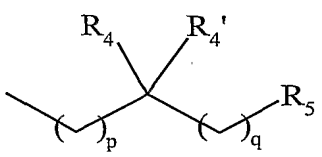
aryloxy

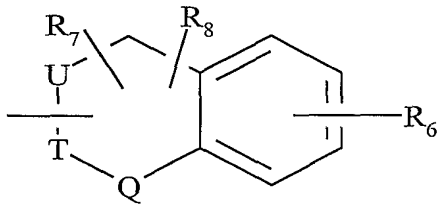
optionally substituted with one or more groups independently selected from the group consisting of hydroxy, halogen, trihalomethyl, alkyl, alkoxy, cyano, nitro, amino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, and cyanoguanidino,

and heteroaryl

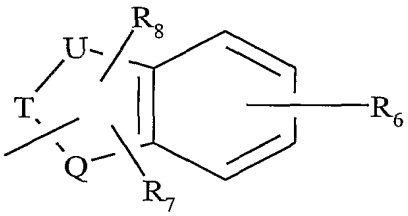
optionally substituted with one or more groups independently selected from the group consisting of hydroxy, halogen, trihalomethyl, alkyl, alkoxy, cyano, nitro, amino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, and cyanoguanidino;

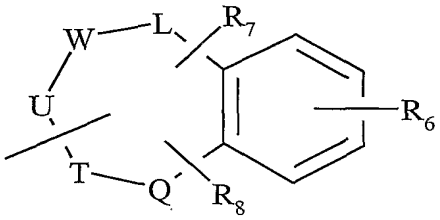
R_1 is:





or





or

p is 0, 1 or 2;

q is 0, 1 or 2;

R_4 and R_4' are independently selected from the group consisting of hydrogen, halogen, alkyl, aryl, heteroaryl

wherein the aryl or heteroaryl is optionally substituted with one or more groups independently selected from the group of consisting of hydrogen, hydroxy, halogen, trihalomethyl, alkyl, alkoxy, cyano, nitro, amino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, and cyanoguanidino;

and COR_9; wherein R_9 is hydroxy, alkyl, alkoxy, amino, alkylamino or arylamino;

R_5 is aryl or heteroaryl

optionally substituted with one or more groups independently selected from the group consisting of hydroxy, halogen, trihalomethyl, alkyl, alkoxy, cyano, nitro, amino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, cyanoguanidino, aryl

optionally substituted with one or more groups independently selected from the group consisting of hydroxy, halogen, trihalomethyl, alkyl, alkoxy, cyano, nitro, amino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, and cyanoguanidino,

and aryloxy

optionally substituted with one or more groups independently selected from the group consisting of hydroxy, halogen, trihalomethyl, alkyl, alkoxy, cyano, nitro, amino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, and cyanoguanidino;

R_6 is selected from the group consisting of hydrogen, hydroxy, halogen, trihalomethyl, alkyl, alkoxy, cyano, nitro, amino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, cyanoguanidino, aryl

optionally substituted with one or more groups independently selected from the group consisting of hydroxy, halogen, trihalomethyl, alkyl, alkoxy, cyano, nitro, amino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl,

alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, and cyanoguanidino,
and aryloxy

optionally substituted with one or more groups independently selected from the group consisting of hydroxy, halogen, trihalomethyl, alkyl, alkoxy, cyano, nitro, amino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, and cyanoguanidino;

R_7 and R_8 are independently selected from the group consisting of hydrogen, hydroxy, halogen, trihalomethyl, alkyl, alkoxy, cyano, nitro, amino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, and cyanoguanidino;

Q, T, U, W and L are independently selected from the group of atoms consisting of C, N, O and S; wherein adjacent atoms U-T, T-Q, U-W, W-L may form one or more double bonds, and no pair of said adjacent atoms forms O-O or S-S;

R_2 is selected from the group consisting of alkyl, alkenyl and alkynyl

optionally substituted with one or more groups independently selected from the group consisting of carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, alkylsulfonylcarbamoyl, arylsulfonylcarbamoyl, alkyloxycarbonyl, tetrazolyl, isoxazolyl, isothiazolyl, alkylsulfonamido, arylsulfonamido, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylsulfonamide, arylsulfonamide, alkylthio, halogen, acyloxy, hydroxy, nitro, amino, acylamino, alkylamino, cyano, aryl

optionally substituted with one or more groups independently selected from the group consisting of alkyl or alkoxy, wherein the alkyl or alkoxy may be

optionally substituted with carboxy or alkyloxycarbonyl, cyano, nitro, amino, acylamino, alkylamino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, alkylsulfonylcarbamoyl, arylsulfonylcarbamoyl, alkyloxycarbonyl, tetrazolyl, isoxazolyl, isothiazolyl, alkylsulfonamido, arylsulfonamido, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylsulfonamide, arylsulfonamide, alkylthio, acyl, acyloxy, aryloxy, arylmethyloxy, hydrazino, hydroxyamino, amidino, guanidino, cyanoguanidino, hydroxy, and halogen,

heteroaryl

optionally substituted with one or more groups independently selected from the group consisting of alkyl or alkoxy which may be optionally substituted with carboxy or alkyloxycarbonyl, cyano, nitro, amino, acylamino, alkylamino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, alkylsulfonylcarbamoyl, arylsulfonylcarbamoyl, alkyloxycarbonyl, tetrazolyl, isoxazolyl, isothiazolyl, alkylsulfonamido, arylsulfonamido, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylsulfonamide, arylsulfonamide, alkylthio, acyl, acyloxy, hydrazino, hydroxyamino, amidino, guanidino, cyanoguanidino, hydroxy, and halogen,

alkoxy

optionally substituted with one or more groups independently selected from the group consisting of alkyl or alkoxy which may be optionally substituted with carboxy or alkyloxycarbonyl, cyano, nitro, amino, acylamino, alkylamino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, alkylsulfonylcarbamoyl, arylsulfonylcarbamoyl, alkyloxycarbonyl, tetrazolyl, isoxazolyl, isothiazolyl, alkylsulfonamido, arylsulfonamido, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylsulfonamide, arylsulfonamide, alkylthio, acyl, acyloxy, hydrazino, hydroxyamino, amidino, guanidino, cyanoguanidino, hydroxy, and halogen,

arylmethyloxy

optionally substituted with one or more groups independently selected from the group consisting of alkyl or alkoxy which is optionally substituted with carboxy or alkyloxycarbonyl, cyano, nitro, amino, acylamino, alkylamino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, alkylsulfonylcarbamoyl, arylsulfonylcarbamoyl, alkyloxycarbonyl, tetrazolyl, isoxazolyl, isothiazolyl, alkylsulfonamido, arylsulfonamido, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylsulfonamide, arylsulfonamide, alkylthio, acyl, acyloxy, hydrazino, hydroxyamino, amidino, guanidino, cyanoguanidino, hydroxy, and halogen,

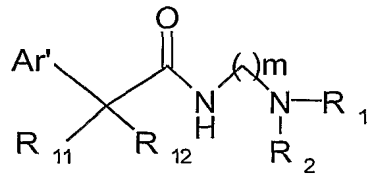
cycloalkyl

optionally substituted with one or more groups independently selected from the group consisting of alkyl or alkoxy which is optionally substituted with carboxy or alkyloxycarbonyl, cyano, nitro, amino, acylamino, alkylamino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, alkylsulfonylcarbamoyl, arylsulfonylcarbamoyl, alkyloxycarbonyl, tetrazolyl, isoxazolyl, isothiazolyl, alkylsulfonamido, arylsulfonamido, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylsulfonamide, arylsulfonamide, alkylthio, acyl, acyloxy, hydrazino, hydroxyamino, amidino, guanidino, cyanoguanidino, hydroxy, and halogen,

and heterocycle;

provided that no bond is formed between R_1 and R_2.

There is also provided, in accordance with a second aspect of the present invention, a compound having Formula (I'):



(I')

or a salt, hydrate, or stereoisomer thereof, wherein:

m is 2, 3, 4 or 5;

R_{11} and R_{12} are independently selected from the group consisting of hydrogen, halogen, C_{1-5} alkyl, aryl and heteroaryl

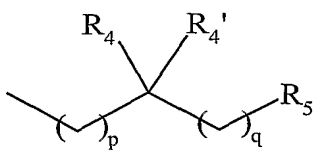
wherein the C_{1-5} alkyl, aryl or heteroaryl is optionally substituted with one or more groups independently selected from the group of consisting of hydrogen, hydroxy, halogen, trihalomethyl, C_{1-5}alkyl, C_{1-5}alkoxy, cyano, nitro, amino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, and cyanoguanidino;

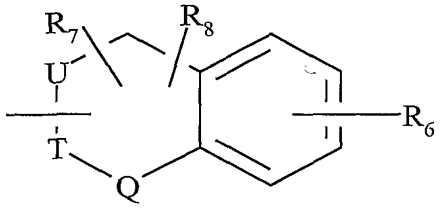
Ar' is aryl or heteroaryl

optionally substituted with one or more groups independently selected from the group consisting of hydroxy, halogen, trihalomethyl, trihalomethoxy, C_{1-5}alkyl, C_{1-5}alkoxy, cyano, nitro, amino, carboxy, alkyloxycarbonyl, arylmethyloxycarbonyl, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, cyanoguanidino, aryl, aryloxy, heteroaryl, benzyloxy, benzoyl and naphthoyl

wherein the aryl, aryloxy, heteroaryl, benzyloxy, benzoyl or naphthoyl is optionally substituted with one or more groups independently selected from the group consisting of hydroxy, halogen, trihalomethyl, C_{1-5}alkyl, C_{1-5} alkoxy, cyano, nitro, amino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, and cyanoguanidino;

R_1 is:





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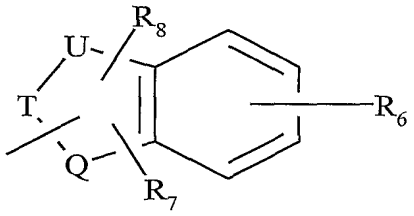

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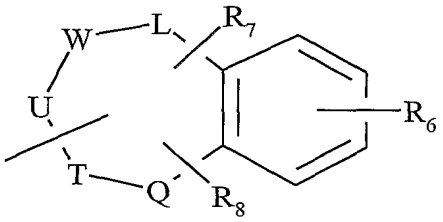


p is 0, 1 or 2;

q is 0, 1 or 2;

R_4 and R_4' are independently selected from the group consisting of hydrogen, halogen, C_{1-5} alkyl, aryl, heteroaryl

wherein the aryl or heteroaryl is optionally substituted with one or more groups independently selected from the group of consisting of hydrogen, hydroxy, halogen, trihalomethyl, C_{1-5} alkyl, C_{1-5}alkoxy, cyano, nitro, amino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, and cyanoguanidino

and COR_9, wherein R_9 is hydroxy, C_{1-5}alkyl, C_{1-5}alkoxy, amino, alkylamino or arylamino;

R_5 is aryl or heteroaryl

optionally substituted with one or more groups independently selected from the group consisting of hydroxy, halogen, trihalomethyl, C_{1-5} alkyl, C_{1-5} alkoxy, cyano, nitro, amino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, cyanoguanidino, aryl, and aryloxy

wherein the aryl or aryloxy is optionally substituted with one or more groups independently selected from the group consisting of hydroxy, halogen, trihalomethyl, C_{1-5} alkyl, C_{1-5} alkoxy, cyano, nitro, amino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, and cyanoguanidino;

R_6 is selected from the group consisting of hydrogen, hydroxy, halogen, trihalomethyl, C_{1-5} alkyl, C_{1-5} alkoxy, cyano, nitro, amino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, cyanoguanidino, aryl and aryloxy

wherein the aryl or aryloxy is optionally substituted with one or more groups independently selected from the group consisting of hydroxy, halogen, trihalomethyl, C_{1-5} alkyl, C_{1-5} alkoxy, cyano, nitro, amino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, and cyanoguanidino;

R_7 and R_8 are independently selected from the group consisting of hydrogen, hydroxy, halogen, trihalomethyl, C_{1-5} alkyl, C_{1-5} alkoxy, cyano, nitro, amino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, and cyanoguanidino;

Q, T, U, W and L are independently selected from the group of atoms consisting of C, N, O and S; wherein adjacent atoms U-T, T-Q, U-W, W-L may form one or more double bonds, and no pair of such adjacent atoms forms O-O or S-S;

R_2 is selected from the group consisting of C_{1-8} alkyl, C_{1-8} alkenyl and C_{1-8} alkynyl

optionally substituted with one or more groups independently selected from the group consisting of carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, alkylsulfonylcarbamoyl, arylsulfonylcarbamoyl, alkyloxycarbonyl, tetrazolyl, isoxazolyl, isothiazolyl, alkylsulfonamido, arylsulfonamido, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylsulfonamide, arylsulfonamide, alkylthio, halogen, acyloxy, hydroxy, nitro, amino, acylamino, alkylamino, cyano, aryl

optionally substituted with one or more groups independently selected from the group consisting of C_{1-5} alkyl or C_{1-5} alkoxy, wherein the alkyl or alkoxy may be optionally substituted with carboxy or alkyloxycarbonyl, cyano, nitro, amino, acylamino, alkylamino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, alkylsulfonylcarbamoyl, arylsulfonylcarbamoyl, alkyloxycarbonyl, tetrazolyl, isoxazolyl, isothiazolyl, alkylsulfonamido, arylsulfonamido, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylsulfonamide, arylsulfonamide, alkylthio, acyl, acyloxy, aryloxy, arylmethyloxy, hydrazino, hydroxyamino, amidino, guanidino, cyanoguanidino, hydroxy, and halogen, heteroaryl

optionally substituted with one or more groups independently selected from the group consisting of C_{1-5} alkyl or C_{1-5} alkoxy which may be optionally substituted with carboxy or alkyloxycarbonyl, cyano, nitro, amino, acylamino, alkylamino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, alkylsulfonylcarbamoyl, arylsulfonylcarbamoyl, alkyloxycarbonyl, tetrazolyl, isoxazolyl, isothiazolyl, alkylsulfonamido, arylsulfonamido, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylsulfonamide, arylsulfonamide, alkylthio, acyl, acyloxy, hydrazino, hydroxyamino, amidino, guanidino, cyanoguanidino, hydroxy, and halogen,

C_{1-5} alkoxy

optionally substituted with one or more groups independently selected from the group consisting of C_{1-5} alkyl or C_{1-5} alkoxy which may be optionally substituted with carboxy or alkyloxycarbonyl, cyano, nitro, amino, acylamino, alkylamino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, alkylsulfonylcarbamoyl, arylsulfonylcarbamoyl, alkyloxycarbonyl, tetrazolyl, isoxazolyl, isothiazolyl, alkylsulfonamido, arylsulfonamido, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylsulfonamide, arylsulfonamide, alkylthio, acyl, acyloxy, hydrazino, hydroxyamino, amidino, guanidino, cyanoguanidino, hydroxy, and halogen,

arylmethyloxy

optionally substituted with one or more groups independently selected from the group consisting of C_{1-5} alkyl or C_{1-5} alkoxy which is optionally substituted with carboxy or alkyloxycarbonyl, cyano, nitro, amino, acylamino, alkylamino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, alkylsulfonylcarbamoyl, arylsulfonylcarbamoyl, alkyloxycarbonyl, tetrazolyl, isoxazolyl, isothiazolyl, alkylsulfonamido, arylsulfonamido, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylsulfonamide, arylsulfonamide, alkylthio, acyl, acyloxy, hydrazino, hydroxyamino, amidino, guanidino, cyanoguanidino, hydroxy, and halogen,

C_{3-7} cycloalkyl

optionally substituted with one or more groups independently selected from the group consisting of C_{1-5} alkyl or C_{1-5} alkoxy which is optionally substituted with carboxy or alkyloxycarbonyl, cyano, nitro, amino, acylamino, alkylamino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, alkylsulfonylcarbamoyl, arylsulfonylcarbamoyl, alkyloxycarbonyl, tetrazolyl, isoxazolyl, isothiazolyl, alkylsulfonamido, arylsulfonamido, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylsulfonamide, arylsulfonamide, alkylthio, acyl, acyloxy, hydrazino, hydroxyamino, amidino, guanidino, cyanoguanidino, hydroxy, and halogen,

and heterocycle;

provided that no bond is formed between R_1 and R_2.

Other embodiments of the present invention relate to a pharmaceutical composition that comprises one or more the above-described compounds, and to treating CCR-3-mediated disease by administering to a patient an effective amount of such a pharmaceutical composition.

In another embodiment, a kit is provided for treating CCR-3 mediated diseases in a patient, comprising (A) a pharmaceutical composition as described above, (B) reagents to effect administration of the pharmaceutical composition to a patient, and (C) instruments to effect administration of the pharmaceutical composition to the patient.

Other features and advantages of the present invention will become apparent from the following detailed description. It should be understood that examples are given by way of illustration only, since various changes and modifications within the spirit and scope of the invention will become apparent to those skilled in the art.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 shows the suppression of eosinophil infiltration in bronchoalveolarl lavage fluid (BALF) by Compound No. 12.

Figure 2 shows the suppression of eosinophil infiltration in bronchoalveolarl lavage fluid (BALF) by Compound No. 87.

Scheme 1 is a representation of the synthesis of N-benzylcarbamoyl-N'-[2-(4-chlorophenyl)ethyl]-N'-ethyl-1,3-diaminopropane (Compound No. 1).

Scheme 2 is a representation of the synthesis of 4-[[3-(2-methylbenzylureido)propyl][1-(4-chlorophenyl)ethyl]amino]butanoic acid (Compound No. 13).

Scheme 3 is a representation of the synthesis of methyl 4-[[3-(2-methylbenzylureido)propyl][1-(4-chlorophenyl)ethyl]amino]butylate (Compound No. 27).

Scheme 4 presents the synthesis of 5-[[3-(2,4-dichlorobenzylureido)propyl][1-(4-chlorophenyl)ethyl]amino]pentanoic acid (Compound No. 47).

Scheme 5 is a representation of the synthesis of [N-(3,4-dichlorophenylcarbamoyl)-N'-[2-(4-chlorophenyl)ethyl]-N'-[2-(2-methoxyethoxy)ethyl]-1,3-diaminopropane (Compound No. 53).

Scheme 6 presents the synthesis of 4-[[3-[(4-Chloroanilino)carbonylamino]propyl](6-methoxy -1-indanyl)amino]butanoic acid (Compound 63).

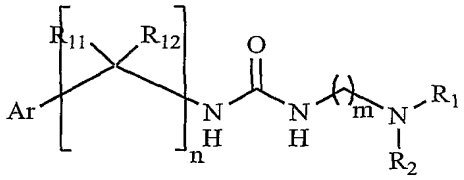
Scheme 7 presents the synthesis of 4-[[3-[2-[4-(Benzyloxy)-3-methoxyphenyl]acetylamino]propyl][1-(4-chlorophenyl)ethyl]amino]butanoic acid (Compound 87).

Scheme 8 represents the formation of the acyl halide of (4-Benzyloxy-3-methoxyphenyl)acetic acid.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

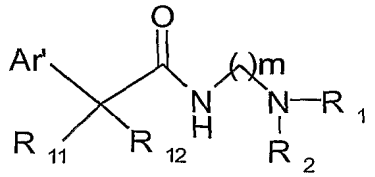
The present invention provides a new class of compounds which inhibit CCR-3 receptor activity. Because the CCR-3 receptor is understood to mediate a variety of diseases, the disclosed compounds, which are derived from urea, are useful for treating CCR-3-mediated diseases. Examples of such diseases include, without limitation, eosinophil-mediated diseases such as asthma, rhinitis, eczema, inflammatory bowl diseases, parasitic infections, and diseases that are mediated by T-cells, mast cells (Ochi H. et al., *J. Exp. Med.* (1999) 190:267-280, Romagnani P. et al., *Am. J. Pathol.* (1999) 155:1195-1204) and/or dendritic cells, such as autoimmune and inflammatory diseases and HIV infection.

In one embodiment of the present invention, there is provided a variety of compounds that inhibit cell function mediated by the chemokine receptor CCR-3. These compounds are urea derivatives with the formula depicted below as Formula I:



(I)

In another embodiment of the present invention, there is provided another variety of compounds that also inhibit cell function mediated by the chemokine receptor CCR-3. These compounds are amide derivatives of Formula (I') as depicted below:



(I')

The compounds of Formula (I) and (I'), as defined above, include variable groups such as an aryl group, a heteroaryl group and a heterocyclic group.

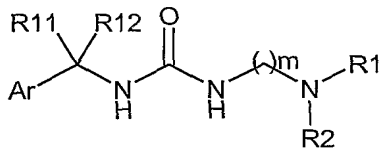
An aryl group is defined as a 6-15 membered aromatic carbocyclic moiety. This includes but is not limited to phenyl, naphthyl, anthryl, indenyl, phenanthrenyl and others.

A heteroaryl group is defined as a 5-15 membered aromatic ring system containing at least one hetero atom selected from the group consisting of N, O, and S. These include but are not limited to 2- or 3-thienyl, 2- or 3-furyl, 2- or 3-pyrrolyl, 2-, 3- or 4-pyridyl, 2-, 4- or 5-oxazolyl, 2-, 4- or 5-thiazolyl, 3-, 4- or 5-pyrazolyl, 2-, 4- or 5-imidazolyl, 3-, 4- or 5- isoxazolyl, 3-, 4- or 5-isothiazolyl, 3- or 5-(1,2,4-oxadiazolyl), 1,3,4-oxadiazolyl, 3- or 5-(1,2,4-thiadiazolyl), 1,3,4-thiadiazolyl, 4- or 5-(1,2,3-thiadiazolyl), 1,2,5-thiadiazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1H- or 2H-tetrazolyl, N-oxido- 2-, 3- or 4- pyridyl, 2-, 4- or 5-pyrimidinyl, N-oxido- 2-, 4- or 5-pyrimidinyl, 3- or 4-pyridazinyl, pyrazinyl, N-oxido-3- or 4-pyridazinyl, benzofuryl, indolyl, benzothiazolyl, benzoxazolyl, triazinyl, oxotriazinyl, tetrazolo[1,5-b]pyridazinyl, triazolo[4,5-b]pyridazinyl, oxoimidazinyl, dioxotriazinyl, pyrrolidinyl, pyranyl, thiopyranyl, 1,4-oxazinyl, 1,4-thiazinyl, 1,3-thiazinyl, benzimidazolyl, quinolyl, isoquinolyl, cinnolinyl, phthalazinyl, quinazolinyl, quinoxalinyl, indolizinyl, quinolizinyl, 1,8-naphthyridinyl, purinyl, pteridinyl, dibenzofuranyl, carbazolyl, acridinyl, phenanthridinyl, phenazinyl, phenothiazinyl and phenoxazinyl.

A heterocyclic group is defined as a 5-15 membered non-aromatic ring system containing at least one hetero atom selected from the group consisting of N, O, and S. These include but are not limited to hydrogenated derivatives of 2- or 3-thienyl, 2- or 3-furyl, 2- or 3- pyrrolyl, 2-, 3- or 4-pyridyl, 2-, 4- or 5-oxazolyl, 2-, 4- or 5-thiazolyl, 3-, 4- or 5-pyrazolyl, 2-, 4- or 5-imidazolyl, 3-, 4- or 5-isoxazolyl, 3-, 4- or 5-isothiazolyl, 3- or 5- (1,2,4-oxadiazolyl), 1,3,4-oxadiazolyl, 3- or 5- (1,2,4-thiadiazolyl), 1,3,4-thiadiazolyl, 4- or 5-(1,2,3-thiadiazolyl), 1,2,5-thiadiazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1H- or 2H-tetrazolyl, N-oxido- 2-, 3-

or 4- pyridyl, 2-, 4- or 5-pyrimidinyl, N-oxido- 2-, 4- or 5- pyrimidinyl, 3- or 4-pyridazinyl, pyrazinyl, N-oxido-3- or 4-pyridazinyl, benzofuryl, indolyl, benzothiazolyl, benzoxazolyl, triazinyl, oxotriazinyl, tetrazolo [1,5-b]pyridazinyl, triazolo[4,5-b]pyridazinyl, oxoimidazinyl, dioxotriazinyl, pyrrolidinyl, pyranyl, thiopyranyl, 1,4-oxazinyl, 1,4-thiazinyl, 1,3-thiazinyl, benzimidazolyl, quinolyl, isoquinolyl, cinnolinyl, phthalazinyl, quinazolinyl, quinoxalinyl, indolizinyl, quinolizinyl, 1,8-naphthyridinyl, purinyl, pteridinyl, dibenzofuranyl, carbazolyl, acridinyl, phenanthridinyl, phenazinyl, phenothiazinyl and phenoxazinyl. The heterocyclic moiety may also include dioxolanyl, morpholinyl, piperidinyl, and piperazinyl.

In another embodiment of the present invention, there is provided a family of compounds which inhibit cell function mediated by the chemokine receptor CCR-3. In general, these compounds have the Formula (II) depicted below:



(II)

or a salt, hydrate, stereoisomer or complex thereof, wherein:

m is 2, 3, 4 or 5;

R11 and R12 are independently selected from the group consisting of hydrogen, halogen, alkyl, aryl and heteroaryl

wherein the alkyl, aryl or heteroaryl is optionally substituted with one or more groups independently selected from the group of consisting of hydrogen, hydroxy, halogen, trihalomethyl, alkyl, alkoxy, cyano, nitro, amino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, and cyanoguanidino;

Ar is aryl or heteroaryl

optionally substituted with one or more groups independently selected from the group consisting of hydroxy, halogen, trihalomethyl, trihalomethoxy, alkyl, alkoxy, cyano, nitro, amino, carboxy, alkyloxycarbonyl, arylmethyloxycarbonyl, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, cyanoguanidino, aryl

optionally substituted with one or more groups independently selected from the group consisting of hydroxy, halogen, trihalomethyl, alkyl, alkoxy, cyano, nitro, amino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, and cyanoguanidino,

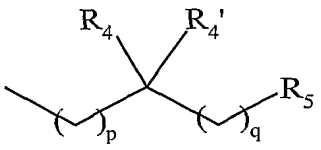
aryloxy

optionally substituted with one or more groups independently selected from the group consisting of hydroxy, halogen, trihalomethyl, alkyl, alkoxy, cyano, nitro, amino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, and cyanoguanidino,

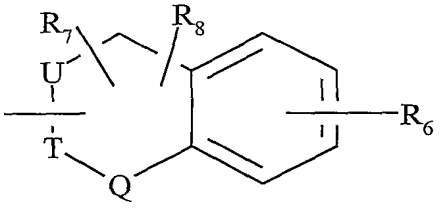
and heteroaryl

optionally substituted with one or more groups independently selected from the group consisting of hydroxy, halogen, trihalomethyl, alkyl, alkoxy, cyano, nitro, amino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, and cyanoguanidino;

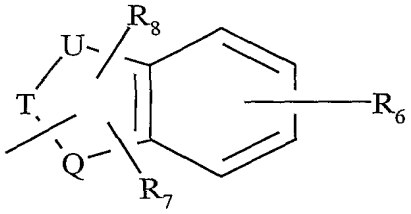
R_1 is:



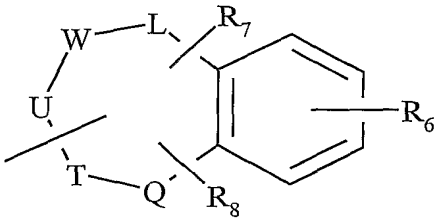
or



or



or



p is 0, 1 or 2;

q is 0, 1 or 2;

R_4 and R_4' are independently selected from the group consisting of hydrogen, halogen, alkyl, aryl, heteroaryl

wherein the aryl or heteroaryl is optionally substituted with one or more groups independently selected from the group of consisting of hydrogen, hydroxy, halogen, trihalomethyl, alkyl, alkoxy, cyano, nitro, amino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, and cyanoguanidino;

and COR_9; wherein R_9 is hydroxy, alkyl, alkoxy, amino, alkylamino or arylamino;

R_5 is aryl or heteroaryl

optionally substituted with one or more groups independently selected from the group consisting of hydroxy, halogen, trihalomethyl, alkyl, alkoxy, cyano, nitro, amino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, cyanoguanidino, aryl

optionally substituted with one or more groups independently selected from the group consisting of hydroxy, halogen, trihalomethyl, alkyl, alkoxy, cyano, nitro, amino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, and cyanoguanidino,

and aryloxy

optionally substituted with one or more groups independently selected from the group consisting of hydroxy, halogen, trihalomethyl, alkyl, alkoxy, cyano, nitro, amino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl,

alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, and cyanoguanidino;

R_6 is selected from the group consisting of hydrogen, hydroxy, halogen, trihalomethyl, alkyl, alkoxy, cyano, nitro, amino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, cyanoguanidino, aryl

optionally substituted with one or more groups independently selected from the group consisting of hydroxy, halogen, trihalomethyl, alkyl, alkoxy, cyano, nitro, amino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, and cyanoguanidino,

and aryloxy

optionally substituted with one or more groups independently selected from the group consisting of hydroxy, halogen, trihalomethyl, alkyl, alkoxy, cyano, nitro, amino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, and cyanoguanidino;

R_7 and R_8 are independently selected from the group consisting of hydrogen, hydroxy, halogen, trihalomethyl, alkyl, alkoxy, cyano, nitro, amino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, and cyanoguanidino;

Q, T, U, W and L are independently selected from the group of atoms consisting of C, N, O and S; wherein adjacent atoms U-T, T-Q, U-W, W-L may

form one or more double bonds, and no pair of such adjacent atoms forms O-O or S-S;

R_2 is selected from the group consisting of alkyl, alkenyl and alkynyl

optionally substituted with one or more groups independently selected from the group consisting of carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, alkylsulfonylcarbamoyl, arylsulfonylcarbamoyl, alkyloxycarbonyl, tetrazolyl, isoxazolyl, isothiazolyl, alkylsulfonamido, arylsulfonamido, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylsulfonamide, arylsulfonamide, alkylthio, halogen, acyloxy, hydroxy, nitro, amino, acylamino, alkylamino, cyano, aryl

optionally substituted with one or more groups independently selected from the group consisting of alkyl or alkoxy, wherein the alkyl or alkoxy may be optionally substituted with carboxy or alkyloxycarbonyl, cyano, nitro, amino, acylamino, alkylamino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, alkylsulfonylcarbamoyl, arylsulfonylcarbamoyl, alkyloxycarbonyl, tetrazolyl, isoxazolyl, isothiazolyl, alkylsulfonamido, arylsulfonamido, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylsulfonamide, arylsulfonamide, alkylthio, acyl, acyloxy, aryloxy, arylmethyloxy, hydrazino, hydroxyamino, amidino, guanidino, cyanoguanidino, hydroxy, and halogen,

heteroaryl

optionally substituted with one or more groups independently selected from the group consisting of alkyl or alkoxy which may be optionally substituted with carboxy or alkyloxycarbonyl, cyano, nitro, amino, acylamino, alkylamino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, alkylsulfonylcarbamoyl, arylsulfonylcarbamoyl, alkyloxycarbonyl, tetrazolyl, isoxazolyl, isothiazolyl, alkylsulfonamido, arylsulfonamido, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylsulfonamide, arylsulfonamide, alkylthio, acyl, acyloxy, hydrazino, hydroxyamino, amidino, guanidino, cyanoguanidino, hydroxy, and halogen,

alkoxy

optionally substituted with one or more groups independently selected from the group consisting of alkyl or alkoxy which may be optionally substituted with carboxy or alkyloxycarbonyl, cyano, nitro, amino, acylamino, alkylamino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, alkylsulfonylcarbamoyl, arylsulfonylcarbamoyl, alkyloxycarbonyl, tetrazolyl, isoxazolyl, isothiazolyl, alkylsulfonamido, arylsulfonamido, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylsulfonamide, arylsulfonamide, alkylthio, acyl, acyloxy, hydrazino, hydroxyamino, amidino, guanidino, cyanoguanidino, hydroxy, and halogen,

arylmethyloxy

optionally substituted with one or more groups independently selected from the group consisting of alkyl or alkoxy which is optionally substituted with carboxy or alkyloxycarbonyl, cyano, nitro, amino, acylamino, alkylamino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, alkylsulfonylcarbamoyl, arylsulfonylcarbamoyl, alkyloxycarbonyl, tetrazolyl, isoxazolyl, isothiazolyl, alkylsulfonamido, arylsulfonamido, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylsulfonamide, arylsulfonamide, alkylthio, acyl, acyloxy, hydrazino, hydroxyamino, amidino, guanidino, cyanoguanidino, hydroxy, and halogen,

cycloalkyl

optionally substituted with one or more groups independently selected from the group consisting of alkyl or alkoxy which is optionally substituted with carboxy or alkyloxycarbonyl, cyano, nitro, amino, acylamino, alkylamino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, alkylsulfonylcarbamoyl, arylsulfonylcarbamoyl, alkyloxycarbonyl, tetrazolyl, isoxazolyl, isothiazolyl, alkylsulfonamido, arylsulfonamido, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylsulfonamide, arylsulfonamide, alkylthio, acyl,

acyloxy, hydrazino, hydroxyamino, amidino, guanidino, cyanoguanidino, hydroxy, and halogen,

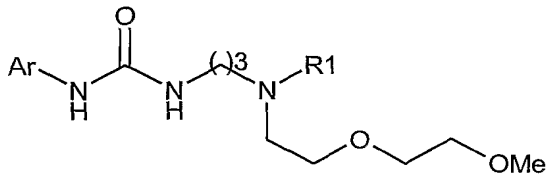
and heterocycle;

provided that no bond is formed between R_1 and R_2.

In another example of the present invention, the family of compounds described above has cycloalkyloxy groups that are C_{3-7} cycloalkyloxy groups, cycloalkyl groups that are C_{3-7} cycloalkyl groups, alkoxy groups that are C_{1-5} alkoxy groups, alkyl groups that are C_{1-8} alkyl groups, alkenyl groups that are C_{1-8} alkenyl groups and alkynyl groups that are

C_{1-8} alkynyl groups.

In another embodiment of the present invention, there is provided another family of compounds which inhibit cell function mediated by the chemokine receptor CCR-3. In general these compounds have the Formula (III) depicted below.



(III)

or a salt, hydrate, stereoisomer, or complex thereof, wherein:

Ar is aryl or heteroaryl

optionally substituted with one or more groups independently selected from the group consisting of hydroxy, halogen, trihalomethyl, trihalomethoxy, alkyl, alkoxy, cyano, nitro, amino, carboxy, alkyloxycarbonyl, arylmethyloxycarbonyl, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, cyanoguanidino, aryl

optionally substituted with one or more groups independently selected from the group consisting of hydroxy, halogen, trihalomethyl, alkyl, alkoxy, cyano, nitro, amino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, and cyanoguanidino,

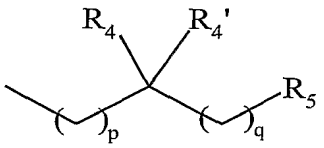
aryloxy

optionally substituted with one or more groups independently selected from the group consisting of hydroxy, halogen, trihalomethyl, alkyl, alkoxy, cyano, nitro, amino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, and cyanoguanidino,

and heteroaryl

optionally substituted with one or more groups independently selected from the group consisting of hydroxy, halogen, trihalomethyl, alkyl, alkoxy, cyano, nitro, amino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, and cyanoguanidino;

R_1 is:



p is 0, 1 or 2;

q is 0, 1 or 2;

R_4 and R_4' are independently selected from the group consisting of hydrogen, halogen, alkyl, aryl, heteroaryl

wherein the aryl or heteroaryl is optionally substituted with one or more groups independently selected from the group of consisting of hydrogen, hydroxy, halogen, trihalomethyl, alkyl, alkoxy, cyano, nitro, amino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, and cyanoguanidino;

and COR_9; wherein R_9 is hydroxy, alkyl, alkoxy, amino, alkylamino or arylamino;

R_5 is aryl or heteroaryl

optionally substituted with one or more groups independently selected from the group consisting of hydroxy, halogen, trihalomethyl, alkyl, alkoxy, cyano, nitro, amino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, cyanoguanidino, aryl

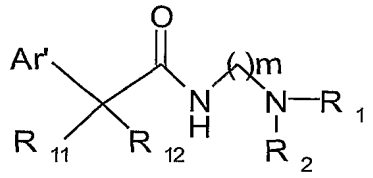
optionally substituted with one or more groups independently selected from the group consisting of hydroxy, halogen, trihalomethyl, alkyl, alkoxy, cyano, nitro, amino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, and cyanoguanidino,

and aryloxy

optionally substituted with one or more groups independently selected from the group consisting of hydroxy, halogen, trihalomethyl, alkyl, alkoxy, cyano, nitro, amino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, and cyanoguanidino.

In another example of the present invention, the family of compounds described above has cycloalkyloxy groups that are C_{3-7} cycloalkyloxy groups, cycloalkyl groups that are C_{3-7} cycloalkyl groups, alkoxy groups that are C_{1-5} alkoxy groups, alkyl groups that are C_{1-8} alkyl groups, alkenyl groups that are C_{1-8} alkenyl groups and alkynyl groups that are C_{1-8} alkynyl groups.

In yet another embodiment of the present invention, there is provided a compound having Formula (II') as depicted below:



(II')

wherein:

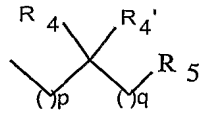
m is 3 or 4;

Ar' is aryl, optionally substituted with one or more groups independently selected from the group consisting of

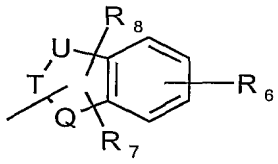
hydroxy, halogen, trihalomethyl, C_{1-5}alkyl, C_{1-5}alkoxy, cyano, nitro, amino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, cyanoguanidino, aryl, aryloxy, benzyloxy, benzoyl, and naphthoyl, wherein the aryl, aryloxy, benzyloxy, benzoyl, or naphthoyl is optionally substituted with one or more groups independently selected from the group consisting of

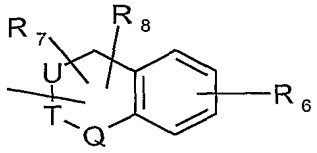
hydroxy, halogen, trihalomethyl, C_{1-5}alkyl, C_{1-5}alkoxy, cyano, nitro, amino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino and cyanoguanidino;

R_1 is:



or





or

p is 0 or 1;

q is 0 or 1;

R_4 and R_4' is hydrogen,halogen,or C_{1-3}alkyl;

R_5 is aryl, optionally substituted with one or more groups independently selected from the group consisting of

hydroxy, halogen, trihalomethyl, C_{1-5}alkyl, C_{1-5}alkoxy, cyano, nitro, amino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, cyanoguanidino;

R_6 is hydrogen, hydroxy, halogen, trihalomethyl, C_{1-5}alkyl, C_{1-5}alkoxy, cyano, nitro, amino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl,

arylsulfamoyl, alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, and cyanoguanidino;

R_7 and R_8 is independently selected from the group consisting of hydrogen, hydroxy, halogen, trihalomethyl, C_{1-5}alkyl, C_{1-5}alkoxy, cyano, nitro, amino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino and cyanoguanidino;

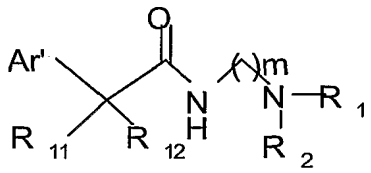
Q, T, U , W and L is independently selected from the group of atoms consisting of C, N, O and S. Two adjacent atoms of Q, T, U, W and L may make double bond(s), and no pair of such adjacent atoms forms O-O or S-S;

R_2 is selected from the group consisting of C_{1-8}alkyl, C_{1-8}alkenyl and C_{1-8}alkynyl, wherein the C_{1-8}alkyl, C_{1-8}alkenyl or C_{1-8}alkynyl is optionally substituted with one or more groups independently selected from the group consisting of carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, alkylsulfonylcarbamoyl, arylsulfonylcarbamoyl, alkyloxycarbonyl, tetrazolyl, isoxazolyl, isothiazolyl, alkylsulfonamido, arylsulfonamido, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylsulfonamide, arylsulfonamide, alkylthio, halogen, hydroxy, nitro, amino, acylamino, alkylamino, cyano;

provided that R_1 and R_2 do not form bond(s) with each other in Formula (II').

R_{11} and R_{12} are independently selected from the group consisting of hydrogen, halogen, and C_{1-3}alkyl.

In still another embodiment of the present invention, there is provided a compound having Formula (III') as depicted below:



(III')

wherein R_2 is selected from the group consisting of

C_{1-5}alkyl, C_{1-5}alkenyl and C_{1-5}alkynyl, optionally substituted with one or more groups independently selected from the group consisting of

carboxy, carbamoyl, alkylcarbamoyl, alkylsulfonylcarbamoyl, alkyloxycarbonyl, tetrazolyl, isoxazolyl, isothiazolyl, alkylsulfonamido, arylsulfonamido, sulfonyl, alkylsulfonyl, sulfamoyl, alkylsulfamoyl, alkylsulfonamide, alkylthio, halogen, hydroxy, nitro, amino, acylamino, alkylamino, cyano,;

R_1 and R_2 do not form bond(s) with one another in Formula (III').

R_4,R_5,R_6,R_7,R_8,R_{11}, R_{12}, U,T,Q,p,and q have the same values as for Formula (II').

In another embodiment of this invention, U, T and Q are carbon atoms; p and q are 0; R_{11} and R_{12} are hydrogen or C_{1-3}alkyl.

Finally, an additional embodiment of the present invention provides for Ar' being aryl, optionally substituted with one or more groups independently selected from the group consisting of:

hydroxy, halogen, trihalomethyl, C_{1-5}alkyl, C_{1-5}alkoxy, cyano, nitro, amino, carboxy, benzyloxy, benzoyl, naphthoyl, aryl, wherein benzyloxy, benzoyl, or naphthoyl is optionally substituted with one or more groups independently selected from the group consisting of:

hydroxy, halogen, trihalomethyl, C_{1-5}alkyl, and C_{1-5}alkoxy.

The compounds of the present invention can be synthesized by various methods including, but not limited to, liquid phase or a solvent based synthesis and solid phase synthesis involving a polymeric resin.

The liquid phase synthesis generally involves addition of a substituted or unsubstituted alkyl amine containing compound to a protected amine containing starting material bearing a leaving group (e.g., Cl, Br, I, OTs, OMs, etc.). The resulting product bearing a protonated amine is reacted with an alkyl halide to yield a substituted amine. Then, the protected amine moiety is deprotected by addition of base or, for example, hydrazine. The resultant free amine is reacted with a compound containing an isocyanate to yield the urea derivative.

A second synthesis involves the reaction of aromatic isocyanate with a haloalkylamine. The resultant product is then further reacted with an optionally substituted amine containing compound, the amine of the optionally substituted amine containing compound is substituted by reaction with an alkyl halide to yield the aromatic urea derivative.

An additional method that can be used to prepare the present compounds involves reaction of a protected amine containing starting compound with an alkylamine. The resultant diamine is reacted with an ester containing a leaving group, after deprotection, the aromatic urea derivative is formed by reaction with a compound containing an aromatic isocyanate.

The aromatic urea derivatives can be further derivatized by conventional organic synthesis techniques, for example, an ester can be converted to an acid by addition of a metal hydroxide. Additionally, salts of the compounds can be formed by conventional synthetic techniques, such as addition to an amine moiety to form an ammonium salt.

Solid phase synthesis involves the use of polymeric resins. Reductive amination of the linker to the resin occurs by reacting a haloalkylamine with the polymeric resin. The protonated amine is then protected by reaction with a substituted or unsubstituted acid chloride. The halogen of the original haloalkylamine is displaced by reaction with an alkyl amine compound and reductive amination follows by reaction with an aldehyde. The protected amine is deprotected by reaction with, for example, tin chloride, an acid or an amine. The deprotected

amine is subsequently reacted with an isocyanate to yield the urea moiety, the product is isolated by working up the reaction mixture, for example, in HCl gas.

A method that can be employed for the synthesis of compounds of formula (I'), as set forth in Scheme 7, involves the reaction of a protected amine-containing compound with an alkylamine. The resultant diamine is reacted with an aldehyde-carboxyl compound. Following deprotection of the protected amine moiety, the resultant compound is reacted with an aromatic acyl halide to give the aromatic amide derivative.

In one embodiment of the present invention, an effective amount of a pharmaceutical composition comprising one or more of the disclosed compounds is administered to a patient suffering from CCR-3 mediated disease. The active compound of the pharmaceutical composition can be administered in a variety of forms, including, but not limited to a salt, a hydrate or a prodrug. In addition, the pharmaceutical composition can optionally contain suitable carriers or excipients.

A "pharmaceutical composition" refers to a mixture of one or more of the compounds described herein, or pharmaceutically acceptable salts, hydrates or prodrugs thereof, with other chemical components, such as physiologically acceptable carriers and excipients. The purpose of a pharmaceutical composition is to facilitate administration of a compound to an organism.

A "prodrug" refers to an agent that is converted into the parent drug in vivo. Prodrugs are often useful because, in some situations, they may be easier to administer than the parent drug. They may be bioavailable by oral administration, for instance, whereas the parent drug may not be. The prodrug also may have improved solubility in pharmaceutical compositions over the parent drug.

As used herein, a "physiologically acceptable carrier" refers to a carrier or diluent that does not cause significant irritation to an organism and does not abrogate the biological activity and properties of the administered compound.

An "excipient" refers to an inert substance added to a pharmaceutical composition to further facilitate administration of a compound. Examples of

excipients include, but are not limited to, calcium carbonate, calcium phosphate, sugars, starches, cellulose derivatives, gelatin, vegetable oils and polyethylene glycol.

The form of the administered compound depends, in part, upon the use or the route of entry. Such forms should allow the agent to reach a target cell whether the target cell is present in a multicellular host or in culture. For example, pharmacological agents or compositions injected into the blood stream should be soluble in the concentrations used. Other factors are known in the art, and include considerations such as toxicity and forms which prevent the compound or composition from exerting its effect.

A compound of the present invention also can be formulated as a pharmaceutically acceptable salt, e.g., acid addition salt, and complexes thereof. The preparation of such salts can facilitate the pharmacological use by altering the physical characteristics of the agent without preventing its physiological effect. Examples of useful alterations in physical properties include, but are not limited to, lowering the melting point to facilitate transmucosal administration and increasing the solubility to facilitate administering higher concentrations of the drug.

A compound of the present invention can be administered to a mammal, including a human patient, using a variety of techniques. For example, for systemic administration, oral administration or injection can be used. For oral administration, a compound of the present invention is formulated into conventional oral administration dosage forms such as capsules, tablets, and tonics. For injection, a compound is formulated in liquid solutions, preferably in physiologically compatible buffers such as Hank's solution or Ringer's solution. In addition, a compound can be formulated in a solid form and redissolved or suspended immediately prior to use. Lyophilized forms can also be produced. Examples of systemic administrations by injection include intramuscularly, intravenously, intraperitoneally and subcutaneously.

Administration also can be by transmucosal or transdermal means. For transmucosal or transdermal administration, penetrants appropriate to the barrier to be permeated are used in the formulation. Such penetrants are generally known in the art, and include, for example, for transmucosal administration, bile salts and fusidic acid derivatives. In addition, detergents may be used to facilitate permeation. Transmucosal administration also can be achieved, for example, by using nasal sprays or suppositories.

Administration of a compound of the present invention can be achieved by any means which transports the compound to the airways and/or lungs of a mammal, including a human patient. In a preferred embodiment, a compound is administered by generating an aerosol comprised of respirable particles, comprising said compound. Delivery is achieved by animal or patient inhalation of the respirable particles. The respirable particles can be liquid or solid and, optionally, can contain other therapeutic ingredients.

For topical administration, the molecules of the invention are formulated into ointments, salves, gels, or creams, as is generally known in the art.

Generally, a therapeutically effective amount for a human patient is between about 10 nmole and 3 mmole of the compound, preferably 1 μmole to 1 mmole. A therapeutically effective amount for a non-human mammal is between about 0.01 and 50 mg/kg, preferably 0.01 and 20 mg/kg. Optimization of the timing and dosage of a disclosed compound is by convention adapted to, among other things, the particular characteristics of the patient or the non-human mammal and the nature and extent of the disease state, and the EC50 or IC50 of the compound. Such adaptations are routine and do not require extraordinary experimentation or skill.

In accordance with yet another aspect of the present invention, there is provided a kit suitable for treating CCR-3 mediated diseases in a patient, comprising a pharmaceutical composition comprising one or more compounds of the present invention, reagents to effect administration of the pharmaceutical composition to the patient and instruments to effect administration of the pharmaceutical composition to

the patient. Examples of such instruments include, but are not limited to application devices, such as syringes or inhalers.

In yet another example, the claimed compounds are useful for treatment and/or prevention of rheumatoid arthritis. The treatment includes, but not limited to, administration of the claimed compounds through subcutaneous, intradermal, intramuscular, intraperitoneal, intravascular, and intracranial injections to human or other mammalian animal bodies.

EXAMPLES

SYNTHESIS OF ACTIVE COMPOUNDS

Example 1. Synthesis of N-Benzylcarbamoyl-N'-[2-(4-chlorophenyl)ethyl]-N'-ethyl-1,3-diaminopropane (Compound 1)

The following synthesis is depicted in Scheme 1.

Step 1: To a mixture of 2-(4-chlorophenyl)ethylamine (1.56 g, 10 mmol) and potassium carbonate (2.8 g, 20 mmol) in CH_3CN (50 ml) was added N-(3-bromopropyl)phthalimide (3.0 g, 11 mmol). The mixture was refluxed under stirring for 16 h, and then filtered. The filtrate was concentrated under vacuum to dryness, and the residue was chromatographed on silica gel (eluting with 2.5% methanol/chloroform) to afford N-[3-[2-(4-chlorophenyl)ethylamino]propyl]phthalimide (2.28 g, 67%): MS(FD) m/e 343 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ 7.84 (m, 2H), 7.71 (m, 2H), 7.24 (d, J = 8.3 Hz, 2H), 7.11 (d, J = 8.3 Hz, 2H), 3.74 (d, J = 6.8 Hz, 2H), 2.82 (t, J = 6.8 Hz, 2H), 2.73 (t, J = 6.8 Hz, 2H), 2.66 (t, J = 6.8 Hz, 2H), 1.84 (m, 2H).

Step 2: To a mixture of N-[3-[2-(4-chlorophenyl)ethylamino]propyl]phthalimide (2.28 g, 6.65 mmol) and potassium carbonate (1.8 g, 13 mmol) in CH_3CN (50 ml) was added ethyl iodide (1.6 ml, 20 mmol). The mixture was stirred at 70 °C for 16 h, and then filtered. The filtrate was concentrated under vacuum to dryness, and the residue was chromatographed on silica gel (eluting with 2% methanol/chloroform) to afford N-[3-[[2-(4-

chlorophenyl)ethyl](ethyl)amino]propyl]phthalimide (1.41 g, 57%): MS(ES^+) m/e 371 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ 7.84 (m, 2H), 7.71 (m, 2H), 7.23 (d, J = 8.5 Hz, 2H), 7.11 (d, J = 8.5 Hz, 2H), 3.71 (t, J = 7.3 Hz, 2H), 2.66 (m, 4H), 2.57 (m, 4H), 1.83 (m, 2H), 1.00 (t, J = 7.1 Hz, 3H).

Step 3: To a solution of N-[3-[[2-(4-chlorophenyl)ethyl](ethyl)amino]propyl]phthalimide (1.41 g, 3.8 mmol) in EtOH (20 ml) was added a solution of hydrazine monohydrate (1.5 g, 30 mmol) in EtOH (5 ml). The solution was stirred at RT for 4h, and then filtered. The filtrate was concentrated under vacuum to dryness. After adding water, the mixture was extracted with chloroform, washed with brine, dried over sodium sulfate, and filtered. Concentrating under vacuum gave N-[2-(4-chlorophenyl)ethyl]-N-ethyl-1,3-diaminopropane (903 mg, 99%) which was used in the next step without further purification.

Step 4: To a solution of N-[2-(4-chlorophenyl)ethyl]-N-ethyl-1,3-diaminopropane (30 mg, 0.125 mmol) in CH_2Cl_2 (1 ml) was added benzyl isocyanate (20 mg, 0.15 mmol). After stirring at RT for 1h, the reaction mixture was adsorbed on a plate of silica gel and the plate was developed with 17% methanol/chloroform to afford N-benzylcarbamoyl-N'-[2-(4-chlorophenyl)ethyl]-N'-ethyl-1,3-diaminopropane (31.4 mg, 67%): MS(ES^-) m/e 408 $[M-H]^-$; ^1H NMR (400 MHz, $CDCl_3$) δ 7.27 (m, 4H), 7.23 (m, 3H), 7.08 (d, J = 8.5 Hz, 2H), 5.64 (br, 1H), 5.15 (br, 1H), 4.33 (d, J = 5.9 Hz, 2H), 3.24 (m, 2H), 2.72 (m, 4H), 2.62 (m, 4H), 1.68 (m, 2H), 1.04 (m, 3H).

Compound 2, N-Benzylcarbamoyl-N'-[2-(4-chlorophenyl)ethyl]-N'-ethyl-1,2-diaminoethane, can be obtained in an analogous manner to that described for compound 1 and contains the following characteristics: MS(ES^-) m/e 394 $[M-H]^-$; ^1H NMR (400 MHz, $CDCl_3$) δ 7.30 (m, 4H), 7.22 (m, 3H), 7.06 (d, J = 8.5 Hz, 2H), 5.08 (br, 1H), 4.67 (br, 1H), 4.31 (d, J = 5.9 Hz, 2H), 3.18 (m, 2H), 2.63 (m, 4H), 2.55(m, 4H), 0.97 (m, 3H).

Compound 44, Methyl 5-[[3-(2,4-dichlorobenzylureido)propyl][1-(4-chlorophenyl)ethyl]amino]pentanoate, can be obtained in an analogous manner to that described for compound 1 and contains the following characteristics: MS(ES^+) m/e 550 $[M+Na]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ 7.36 (m, 2H), 7.26 (bs, 4H), 7.20 (m, 1H), 5.03 (br, 1H), 4.40 (d, J = 6.1 Hz, 2H), 3.88 (m, 1H), 3.61 (s, 3H), 3.21 (m, 2H), 2.44 (m, 3H), 2.29 (m, 3H), 1.62 (m, 3H), 1.45 (m, 3H), 1.29 (d, J = 6.8 Hz, 3H).

Compound 45, Ethyl 6-[[3-(2,4-dichlorobenzylureido)propyl][1-(4-chlorophenyl)ethyl]amino]hexanoate, can be obtained in an analogous manner to that described for compound 1 and contains the following characteristics: MS(ES^+) m/e 578 $[M+Na]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ 7.35 (m, 2H), 7.26 (bs, 4H), 7.21 (dd, J = 8.3, 2.2 Hz, 1H), 4.72 (br, 1H), 4.38 (d, J = 6.1 Hz, 2H), 4.10 (q, J = 7.1 Hz, 2H), 3.85 (m, 1H), 3.15 (m, 2H), 2.43 (m, 4H), 2.27 (t, J = 7.3 Hz, 2H), 1.58 (m, 4H), 1.43 (m, 2H), 1.26 (m, 5H).

Compound 46, N-(2,4-Dichlorobenzylcarbamoyl)-N'-[1-(4-chlorophenyl)ethyl]-N'-ethyl-1,3-diaminopropane, can be obtained in an analogous manner to that described for compound 1 and contains the following characteristics: MS(ES^+) m/e 442 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ 7.35 (m, 2H), 7.29 (bs, 4H), 7.20 (m, 1H), 5.19 (m, 1H), 4.91 (br, 1H), 4.37 (d, J = 6.1 Hz, 2H), 3.89 (m, 1H), 3.15 (m, 2H), 2.63 (m, 1H), 2.51 (m, 3H), 1.62 (m, 2H), 1.35 (d, J = 6.6 Hz, 3H), 1.05 (m, 3H).

Example 2. Synthesis of 4-[[3-(2-Methylbenzylureido)propyl][1-(4-chlorophenyl)ethyl]amino]butanoic acid (Compound 13)

The following synthesis is depicted in Scheme 2.

Step 1: N-(3-bromopropyl)phthalimide (3.5 g, 13 mmol) was added to a mixture of 1-(4-chlorophenyl)ethylamine (1.56 g, 10 mmol) and potassium carbonate (1.8 g, 13 mmol) in CH_3CN (50 ml). The mixture was stirred at 70 °C for 16 h, and then filtered. The filtrate was concentrated under vacuum to dryness, and the residue was chromatographed on silica gel (eluting with 1.5%

methanol/chloroform) to afford N-[3-[1-(4-chlorophenyl)ethylamino]propyl]phthalimide (2.1 g, 47%): MS(ES^+) m/e 343 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ 7.83 (m, 2H), 7.72 (m, 2H), 7.23 (d, J = 1.5 Hz, 4H), 3.73 (m, 3H), 2.50 (m, 1H), 2.44 (m, 1H), 1.83 (m, 2H), 1.32 (d, J = 6.6 Hz, 3H).

Step 2: To a solution of N-[3-[1-(4-chlorophenyl)ethylamino]propyl]phthalimide (1.4 g, 4.1 mmol) in 20% EtOH/DMF (50 ml) were added succinic semialdehyde (15 wt.% solution in water, 5.0 ml, 8.2 mmol) and BAP (0.80 ml, 8.2 mmol), and the mixture was stirred at RT for 16 h. After adding water, the mixture was extracted with chloroform, washed with water and brine, dried over sodium sulfate, and filtered. The filtrate was concentrated under vacuum to dryness, and the residue was chromatographed on silica gel (eluting with 5% methanol/chloroform) to afford 4-[[(3-phthalimido)propyl][1-(4-chlorophenyl)ethyl]amino]butanoic acid (1.32 g, 75%): MS(ES^+) m/e 429 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ 7.84 (m, 2H), 7.75 (m, 2H), 7.26 (m, 4H), 4.05 (q, J = 6.8 Hz, 1H), 3.68 (m, 2H), 2.81 (m, 2H), 2.69 (m, 1H), 2.58 (m, 1H), 2.44 (t, J = 5.9 Hz, 2H), 2.01 (m, 2H), 1.82 (m, 2H), 1.51 (d, J = 6.8 Hz, 3H).

Step 3: To a solution of 4-[[(3-phthalimido)propyl][1-(4-chlorophenyl)ethyl]amino]butanoic acid (50 mg, 0.12 mmol) in EtOH (2 ml) was added hydrazine monohydrate (17 µl, 0.35 mmol), and the mixture was stirred at RT for 4 h. After adding chloroform (2 ml) and MeOH (1 ml), the reaction mixture was filtered, and the filtrate was concentrated under vacuum to dryness. After adding chloroform (1.5 ml) and DMF (0.7 ml) to the residue, 2-methylbenzyl isocyanate (28 µl, 0.20 mmol) was added, and the mixture was stirred at RT for 16 h. After adding water, the mixture was extracted with 10% methanol/chloroform, dried over sodium sulfate, and filtered. The filtrate was concentrated under vacuum to dryness. The residue was adsorbed on a plate of silica gel and then developed with 17% methanol/chloroform to afford 4-[[3-(2-methylbenzylureido)propyl][1-(4-

chlorophenyl)ethyl]amino]butanoic acid (24 mg, 45%): MS(ES^+) m/e 468 $[M+Na]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ 7.33 (m, 2H), 7.28 (m, 2H), 7.09 (m, 4H), 6.30 (br, 1H), 4.33 (d, J = 3.4 Hz, 2H), 4.14 (q, J = 6.8 Hz, 1H), 3.19 (m, 2H), 2.92 (m, 1H), 2.82-2.65 (m, 3H), 2.31 (s, 3H), 2.30 (m, 2H), 1.84-1.67 (m, 4H), 1.50 (d, J = 6.8 Hz, 3H).

Compound 4, 4-[[3-[1-(4-Bromophenyl)ethylureido]propyl](1,2,3,4-tetrahydro-1-naphthyl)amino]butanoic acid, can be obtained in an analogous manner to that described for compound 13 and contains the following characteristics: MS(ES^-) m/e 514 $[M+H]^+$; ^1H NMR (400 MHz, DMSO-*d6*) δ 9.52 (br, 1H), 7.67 (br, 1H), 7.49 (m, 3H), 7.24 (m, 5H), 6.35 (br, 1H), 4.90 (m, 1H), 4.69 (m, 1H), 3.14 (m, 1H), 2.88 (m, 1H), 2.71 (m, 8H), 2.08 (m, 2H), 1.92 (m, 3H), 1.63 (m, 3H), 1.29 (m, 3H).

Compound 5, 4-[[3-(2,5-Dichlorobenzylureido)propyl](1,2,3,4-tetrahydro-1-naphthyl)amino]butanoic acid, can be obtained in an analogous manner to that described for compound 13 and contains the following characteristics: MS(ES^+) m/e 492 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ 7.59 (d, J = 7.3 Hz, 1H), 7.33 (d, J = 8.3 Hz, 1H), 7.26 (d, J = 2.2 Hz, 1H), 7.18 (m, 2H), 7.12 (m, 2H), 6.83 (br, 2H), 4.54 (m, 1H), 4.36 (d, J = 3.9 Hz, 2H), 3.24 (m, 2H), 3.09 (m, 1H), 2.74 (m, 5H), 2.43 (m, 1H), 2.12 (m, 2H), 2.01-1.83 (m, 4H), 1.77 (m, 1H), 1.65 (m, 2H).

Compound 6: MS(ES^+) m/e 404 $[M+H]^+$

Compound 7: MS(ES^+) m/e 420 $[M+H]^+$

Compound 8: MS(ES^+) m/e 386 $[M+H]^+$

Compound 9, N-(2-Chlorobenzylcarbamoyl)-N'-[1-(4-chlorophenyl)ethyl]-N'-butyl-1,3-diaminopropane, can be obtained in an analogous manner to that described for compound 13 and contains the following characteristics: MS(ES^+) m/e 436 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ 7.41 (m, 1H), 7.35 (m, 1H), 7.22 (m, 8H), 4.42 (d, J = 6.1 Hz, 2H), 3.88 (m, 1H), 3.16 (m, 2H), 2.45 (m, 4H), 1.42 (m, 2H), 1.25 (m, 7H), 0.87 (t, J = 7.3 Hz, 3H).

Compound 10, 4-[[3-(2-Chlorobenzylureido)propyl][1-(4-fluorophenyl)ethyl]amino]butanoic acid, can be obtained in an analogous manner to that described for compound 13 and contains the following characteristics: MS(ES$^+$) m/e 450 $[M+H]^+$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (m, 1H), 7.35 (m, 2H), 7.29 (m, 1H), 7.16 (m, 3H), 7.07 (t, J = 8.5 Hz, 2H), 6.52 (m, 1H), 4.44 (d, J = 5.4 Hz, 2H), 4.24 (q, J = 6.8 Hz, 1H), 3.22 (m, 2H), 2.98 (m, 1H), 2.82-2.74 (m, 3H), 2.35 (m, 2H), 1.84 (m, 4H), 1.55 (d, J = 6.8 Hz, 3H).

Compound 11, 4-[[3-(2-Chlorobenzylureido)propyl][1-(4-chlorophenyl)ethyl]amino]butanoic acid, can be obtained in an analogous manner to that described for compound 13 and contains the following characteristics: MS(ES$^+$) m/e 488 $[M+Na]^+$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (m, 1H), 7.35 (d, J = 8.5 Hz, 2H), 7.30 (m, 3H), 7.16 (m, 3H), 6.43 (br, 1H), 4.44 (d, J = 4.6 Hz, 2H), 4.19 (q, J = 6.8 Hz, 1H), 3.21 (m, 2H), 2.95 (m, 1H), 2.82-2.72 (m, 3H), 2.34 (m, 2H), 1.83 (m, 4H), 1.53 (d, J = 6.8 Hz, 3H).

Compound 12, 4-[[3-(2,4-Dichlorobenzylureido)propyl][1-(4-chlorophenyl)ethyl]amino]butanoic acid, can be obtained in an analogous manner to that described for compound 13 and contains the following characteristics: MS(ES$^+$) m/e 522 $[M+Na]^+$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (m, 3H), 7.31 (m, 3H), 7.16 (m, 1H), 6.69 (br, 1H), 4.39 (d, J = 4.6 Hz, 2H), 4.22 (q, J = 6.8 Hz, 1H), 3.21 (m, 2H), 2.96 (m, 1H), 2.87-2.75 (m, 3H), 2.36 (m, 2H), 1.84 (m, 4H), 1.56 (d, J = 6.8 Hz, 3H).

Compound 14, 4-[[3-(3-Methylbenzylureido)propyl][1-(4-chlorophenyl)ethyl]amino]butanoic acid, can be obtained in an analogous manner to that described for compound 13 and contains the following characteristics: MS(ES$^+$) m/e 468 $[M+Na]^+$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 (m, 2H), 7.28 (m, 2H), 7.11 (m, 3H), 7.00 (d, J = 7.1 Hz, 1H), 6.31 (br, 1H), 4.31 (bs, 2H), 4.15 (q, J= 6.8 Hz, 1H), 3.20 (m, 1H), 2.91 (m, 1H), 2.82-2.67 (m, 3H), 2.33 (m, 2H), 2.29 (s, 3H), 1.84-1.68 (m, 4H), 1.51 (d, J = 6.8 Hz, 3H).

Compound 15, 4-[[3-(4-Methylbenzylureido)propyl][1-(4-chlorophenyl)ethyl]amino]butanoic acid, can be obtained in an analogous manner to that described for compound 13 and contains the following characteristics: MS(ES$^+$) m/e 468 [M+Na]$^+$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 (d, J = 8.5 Hz, 2H), 7.28 (d, J = 8.5 Hz, 2H), 7.18 (d, J = 7.8 Hz, 2H), 7.07 (d, J = 7.8 Hz, 2H), 6.30 (br, 1H), 4.30 (bs, 2H), 4.15 (q, J = 6.8 Hz, 1H), 3.19 (m, 2H), 2.91 (m, 1H), 2.82-2.66 (m, 3H), 2.32 (m, 2H), 2.28 (s, 3H), 1.84-1.68 (m, 4H), 1.51 (d, J = 6.8 Hz, 3H).

Compound 16, 4-[[3-(3,4-Dichlorobenzylureido)propyl][1-(4-chlorophenyl)ethyl]amino]butanoic acid, can be obtained in an analogous manner to that described for compound 13 and contains the following characteristics: MS(ES$^+$) m/e 522 [M+Na]$^+$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (d, J = 2.0 Hz, 1H), 7.36 (d, J = 8.5 Hz, 2H), 7.33 (d, J = 8.3 Hz, 1H), 7.30 (d, J = 8.5 Hz, 2H), 7.15 (dd, J = 8.3, 2.0 Hz, 1H), 6.89 (br, 1H), 4.30 (bs, 2H), 4.23 (q, J = 6.8 Hz, 1H), 3.21 (m, 2H), 2.96 (m, 1H), 2.88-2.76 (m, 3H), 2.36 (m, 2H), 1.82 (m, 4H), 1.56 (d, J = 6.8 Hz, 3H).

Compound 17, 4-[[3-(4-Methoxybenzylureido)propyl][1-(4-chlorophenyl)ethyl]amino]butanoic acid, can be obtained in an analogous manner to that described for compound 13 and contains the following characteristics: MS(ES$^+$) m/e 484 [M+Na]$^+$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 (d, J = 8.5 Hz, 2H), 7.29 (d, J = 8.5 Hz, 2H), 7.22 (d, J = 8.5 Hz, 2H), 6.80 (d, J = 8.5 Hz, 2H), 6.26 (br, 1H), 4.27 (bs, 2H), 4.16 (q, J = 6.8 Hz, 1H), 3.75 (s, 3H), 3.19 (m, 2H), 2.91 (m, 1H), 2.83-2.67 (m, 3H), 2.32 (m, 2H), 1.84-1.68 (m, 4H), 1.52 (d, J = 6.8 Hz, 3H).

Compound 18, 4-[[3-(4-Bromobenzylureido)propyl][1-(4-chlorophenyl)ethyl]amino]butanoic acid, can be obtained in an analogous manner to that described for compound 13 and contains the following characteristics: MS(ES$^+$) m/e 532 [M+Na]$^+$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (m, 4H), 7.30 (d, J = 8.5 Hz, 2H), 7.19 (d, J = 8.3 Hz, 2H), 6.60 (br, 1H), 4.29 (bs, 2H), 4.21 (q, J = 6.8

Hz, 1H), 3.20 (m, 2H), 2.94 (m, 1H), 2.85-2.70 (m, 3H), 2.33 (m, 2H), 1.84-1.67 (m, 4H), 1.54 (d, J = 6.8 Hz, 3H).

Compound 28, 4-[[3-(Benzylureido)propyl][1-(4-chlorophenyl)ethyl]amino]butanoic acid, can be obtained in an analogous manner to that described for compound 13 and contains the following characteristics: MS(ES^+) m/e 454 $[M+Na]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ 7.34 (d, J = 8.5 Hz, 2H), 7.30 (m, 6H), 7.18 (m, 1H), 6.46 (br, 1H), 4.35 (bs, 2H), 4.16 (q, J = 6.8 Hz, 1H), 3.20 (m, 2H), 2.92 (m, 1H), 2.74 (m, 3H), 2.32 (m, 2H), 1.84-1.68 (m, 4H), 1.51 (d, J = 6.8 Hz, 3H).

Compound 30, 4-[[3-(2,4-Dichlorobenzylureido)propyl](5-chloro-1-indanyl)amino]butanoic acid, can be obtained in an analogous manner to that described for compound 13 and contains the following characteristics: MS(ES^+) m/e 512 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ 7.47 (d, J = 8.1 Hz, 1H), 7.37 (d, J = 8.3 Hz, 1H), 7.30 (m, 1H), 7.26 (m, 2H), 7.17 (m, 2H), 6.60 (br, 1H), 6.55 (br, 1H), 4.78 (m, 1H), 4.40 (d, J = 5.9 Hz, 2H), 3.24 (m, 2H), 2.97 (m, 3H), 2.74 (m, 3H), 2.54 (m, 1H), 2.32 (m, 1H), 2.24 (m, 1H), 2.12 (m, 1H), 1.92 (m, 2H), 1.85 (m, 1H), 1.70 (m, 1H).

Compound 31, 4-[[3-(2,4-Dichlorobenzylureido)propyl][1-(3-chlorophenyl)ethyl]amino]butanoic acid, can be obtained in an analogous manner to that described for compound 13 and contains the following characteristics: MS(ES^+) m/e 500 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ 7.40 (br, 1H), 7.32 (m, 4H), 7.28 (d, J = 2.0 Hz, 1H), 7.13 (m, 1H), 6.69 (br, 1H), 4.35 (m, 2H), 4.24 (q, J = 6.8 Hz, 1H), 3.20 (m, 2H), 3.03 (m, 1H), 2.86 (m, 3H), 2.34 (m, 2H), 1.86 (m, 4H), 1.58 (d, J = 6.8 Hz, 3H).

Compound 32, 4-[[3-(2,4-Dichlorobenzylureido)propyl][1-(2-chlorophenyl)ethyl]amino]butanoic acid, can be obtained in an analogous manner to that described for compound 13 and contains the following characteristics: MS(ES^+) m/e 522 $[M+Na]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ 7.62 (br, 1H), 7.43 (m, 1H), 7.37 (d, J = 8.3 Hz, 1H), 7.31 (m, 3H), 7.16 (m, 1H), 6.70 (br, 1H), 4.77 (q, J =

6.8 Hz, 1H), 4.40 (d, J = 4.1 Hz, 2H), 3.25 (m, 2H), 3.11 (m, 1H), 2.88 (m, 3H), 2.45 (m, 1H), 2.32 (m, 1H), 1.88 (m, 3H), 1.75 (m, 1H), 1.58 (d, J = 6.8 Hz, 3H).

Compound 33, 4-[[3-(2,4-Dichlorobenzylureido)propyl](1,2,3,4-tetrahydro-1-naphthyl)amino]butanoic acid, can be obtained in an analogous manner to that described for compound 13 and contains the following characteristics: MS(ES^+) m/e 492 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ 7.62 (d, J = 7.3 Hz, 1H), 7.36 (d, J = 8.3 Hz, 1H), 7.20 (m, 3H), 7.13 (m, 2H), 6.89 (br, 1H), 4.57 (m, 1H), 4.38 (d, J = 3.4 Hz, 2H), 3.26 (m, 2H), 3.13 (m, 1H), 2.87 (m, 1H), 2.76 (m, 4H), 2.43 (dd, J = 16.6, 5.6 Hz, 1H), 2.13 (m, 2H), 1.94 (m, 4H), 1.75 (m, 1H), 1.66 (m, 2H).

Compound 34, 4-[[3-(2,4-Dichlorobenzylureido)propyl][(1*R*)-1-(4-chlorophenyl)ethyl]amino]butanoic acid, can be obtained in an analogous manner to that described for compound 13 and contains the following characteristics: MS(ES^+) m/e 500 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ 7.35 (m, 3H), 7.30 (m, 3H), 7.16 (dd, J = 8.3, 2.0 Hz, 1H), 6.83 (br, 1H), 4.39 (d, J = 5.1 Hz, 2H), 4.20 (q, J = 6.8 Hz, 1H), 3.19 (m, 2H), 2.95 (m, 1H), 2.78 (m, 3H), 2.35 (m, 2H), 1.80 (m, 4H), 1.54 (d, J = 6.8 Hz, 3H).

Compound 35, 4-[[3-(2,4-Dichlorobenzylureido)propyl][(1*S*)-1-(4-chlorophenyl)ethyl]amino]butanoic acid, can be obtained in an analogous manner to that described for compound 13 and contains the following characteristics: MS(ES^+) m/e 500 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ 7.35 (m, 3H), 7.30 (m, 3H), 7.16 (dd, J = 8.3, 2.2 Hz, 1H), 6.84 (br, 1H), 4.39 (d, J = 5.1 Hz, 2H), 4.19 (q, J = 6.8 Hz, 1H), 3.19 (m, 2H), 2.95 (m, 1H), 2.78 (m, 3H), 2.36 (m, 2H), 1.80 (m, 4H), 1.53 (d, J = 6.8 Hz, 3H).

Compound 36, 4-[[3-(2,4-Dichlorobenzylureido)propyl](7-methoxy-1,2,3,4-tetrahydro-1-naphthyl)amino]butanoic acid, can be obtained in an analogous manner to that described for compound 13 and contains the following characteristics: MS(ES^+) m/e 522 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ 7.35 (d, J = 8.3 Hz,

1H), 7.28 (d, J = 2.0 Hz, 1H), 7.20 (d, J = 2.4 Hz, 1H), 7.14 (dd, J = 8.3, 2.2 Hz, 1H), 7.04 (d, J = 8.5 Hz, 1H), 6.82 (br, 2H), 6.79 (dd, J = 8.5, 2.4 Hz, 1H), 4.52 (t, J = 7.3 Hz, 1H), 4.37(d, J = 5.1 Hz, 2H), 3.71 (s, 3H), 3.26 (m, 2H), 3.15 (m, 1H), 2.85 (m, 1H), 2.75 (m, 2H), 2.68 (m, 2H), 2.46 (m, 1H), 2.12 (m, 2H), 1.95 (m, 4H), 1.68 (m, 3H).

Compound 37, 4-[[3-(2,4-Dichlorobenzylureido)propyl][(1*S*)-1-(4-methylphenyl)ethyl]amino]butanoic acid, can be obtained in an analogous manner to that described for compound 13 and contains the following characteristics: MS(ES^+) m/e 502 $[M+Na]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ 7.38 (d, J = 8.3 Hz, 1H), 7.30 (d, J = 2.2 Hz, 1H), 7.24 (d, J = 8.3 Hz, 2H), 7.18 (d, J = 8.1 Hz, 2H), 7.15 (dd, J = 8.3, 2.0 Hz, 1H), 7.06 (br, 1H), 4.40 (d, J = 5.4 Hz, 2H), 4.25 (q, J = 6.8 Hz, 1H), 3.24 (m, 2H), 3.07 (m, 1H), 2.88 (m, 2H), 2.80 (m, 1H), 2.37 (m, 2H), 2.35 (s, 3H), 1.88 (m, 3H), 1.75 (m, 1H), 1.60 (d, J = 6.8 Hz, 3H).

Compound 38, 4-[[3-(2,4-Dichlorobenzylureido)propyl][(1*S*)-1-(4-methoxylphenyl)ethyl]amino]butanoic acid, can be obtained in an analogous manner to that described for compound 13 and contains the following characteristics: MS(ES^+) m/e 518 $[M+Na]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ 7.38 (d, J = 8.3 Hz, 1H), 7.28 (m, 3H), 7.16 (dd, J = 8.3, 2.2 Hz, 1H), 7.02 (br, 1H), 6.90 (d, J = 8.8 Hz, 2H), 4.40 (d, J = 5.4 Hz, 2H), 4.27 (m, 1H), 3.80 (s, 3H), 3.24 (m, 2H), 3.05 (m, 1H), 2.87 (m, 2H), 2.82 (m, 1H), 2.35 (m, 2H), 1.89 (m, 3H),1.77 (m, 1H), 1.60 (d, J = 6.8 Hz, 3H).

Compound 39, 4-[[3-(2,4-Dichlorobenzylureido)propyl](1-indanyl)amino]butanoic acid, can be obtained in an analogous manner to that described for compound 13 and contains the following characteristics: MS(ES^+) m/e 478 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ 7.38 (d, J = 8.3 Hz, 1H), 7.30 (m, 3H), 7.22 (m, 1H), 7.15 (dd, J = 8.3, 2.0 Hz, 1H), 7.01 (br, 1H), 6.93 (m, 1H), 4.88 (m, 1H), 4.40 (d, J = 5.6 Hz, 2H), 3.26 (m, 2H), 3.02 (m, 3H), 2.77 (m, 3H), 2.53 (dd, J = 16.8, 6.8 Hz, 1H), 2.35 (m, 1H), 2.21 (m, 1H), 2.13 (m, 1H), 1.93 (m, 3H), 1.71 (m, 1H).

Compound 40, 4-[[3-(2,4-Dichlorobenzylureido)propyl][1-(4-fluorophenyl)ethyl]amino]butanoic acid, can be obtained in an analogous manner to that described for compound 13 and contains the following characteristics: MS(ES^+) m/e 484 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ 7.36 (m, 3H), 7.31 (d, J = 2.0 Hz, 1H), 7.16 (dd, J = 8.3, 2.0 Hz, 1H), 7.08 (t, J = 8.5 Hz, 2H), 6.80 (br, 1H), 4.39 (d, J = 5.4 Hz, 2H), 4.26 (q, J = 6.8 Hz, 1H), 3.22 (m, 2H), 2.99 (m, 1H), 2.81 (m, 3H), 2.35 (m, 2H), 1.83 (m, 4H), 1.57 (d, J = 6.8 Hz, 3H).

Compound 41, N-(2,4-Dichlorobenzylcarbamoyl)-N'-[1-(4-chlorophenyl)ethyl]-N'-butyl-1,3-diaminopropane, can be obtained in an analogous manner to that described for compound 13 and contains the following characteristics: MS(ES^+) m/e 470 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ 7.33 (m, 2H), 7.27 (bs, 4H), 7.19 (m, 1H), 4.85 (br, 1H), 4.36 (d, J = 6.1 Hz, 2H), 3.88 (q, J = 6.8 Hz, 1H), 3.13 (m, 2H), 2.45 (m, 4H), 1.58 (m, 2H), 1.43 (m, 2H), 1.32 (d, J = 6.6 Hz, 3H), 1.26 (m, 2H), 0.87 (t, J = 7.3 Hz, 3H).

Compound 42, 4-[[4-(2,4-Dichlorobenzylureido)butyl][1-(4-chlorophenyl)ethyl]amino]butanoic acid, can be obtained in an analogous manner to that described for compound 13 and contains the following characteristics: MS(ES^+) m/e 536 $[M+Na]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ 7.36 (m, 3H), 7.30 (m, 3H), 7.15 (dd, J = 8.3, 2.0 Hz, 1H), 6.72 (m, 1H), 6.45 (br, 1H), 4.38 (d, J = 5.1 Hz, 2H), 4.23 (q, J = 6.8 Hz, 1H), 3.17 (m, 2H), 2.84 (m, 2H), 2.73 (m, 1H), 2.60 (m, 1H), 2.39 (m, 2H), 1.80 (m, 2H), 1.67 (m, 2H), 1.54 (d, J = 7.1 Hz, 3H), 1.45 (m, 2H).

Compound 43, 4-[[5-(2,4-Dichlorobenzylureido)pentyl][1-(4-chlorophenyl)ethyl]amino]butanoic acid, can be obtained in an analogous manner to that described for compound 13 and contains the following characteristics: MS(ES^+) m/e 550 $[M+Na]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ 7.38 (m, 3H), 7.33 (d, J = 8.8 Hz, 2H), 7.29 (d, J = 2.2 Hz, 1H), 7.16 (m, 1H), 6.67 (br, 1H), 6.35 (br, 1H), 4.39 (d, J = 5.4 Hz, 2H), 4.29 (q, J = 6.8 Hz, 1H), 3.19 (m, 2H), 2.83 (m, 2H),

2.68 (m, 2H), 2.42 (m, 1H), 2.35 (m, 1H), 1.81 (m, 2H), 1.67 (m, 2H), 1.58 (d, J = 7.1 Hz, 3H), 1.46 (m, 4H).

Compounds 6-8 can be obtained in an analogous manner to that of Compound 13.

Example 3. Synthesis of Methyl 4-[[3-(2-methylbenzylureido)propyl][1-(4-chlorophenyl)ethyl]amino]butylate (Compound 27)

The following synthesis is depicted in Scheme 3.

To a mixture of 50% KOH (6 ml) and ether (6 ml) was added 1-methyl-3-nitro-1-nitrosoguamidine (0.5 g, 3.4 mmol) at 0 °C. After standing at 0 °C for 5 min, the organic layer was transferred to another Erlenmeyer flask at 0 °C, and KOH pellets (0.5 g) was added. After standing at 0 °C for 5 min, the supernatant (1 ml) was added to a solution of 4-[[3-(2-methylbenzylureido)propyl][1-(4-chlorophenyl)ethyl]amino]butanoic acid (Compound 13, 16 mg, 0.04 mmol) in CH_2Cl_2 (2 ml) at 0 °C. After stirring at 0 °C for 30 min, the reaction mixture was concentrated under vacuum to dryness, and the residue was adsorbed on a plate of silica gel and then developed with 10% methanol/chloroform to afford Methyl 4-[[3-(2-methylbenzylureido)propyl][1-(4-chlorophenyl)ethyl]amino]butylate (16 mg, 90%): MS(ES^+) m/e 482 $[M+Na]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ 7.24 (m, 5H), 7.16 (m, 3H), 4.81 (br, 1H), 4.59 (br, 1H), 4.33 (d, J = 5.4 Hz, 2H), 3.86 (q, J = 6.8 Hz, 1H), 3.59 (s, 3H), 3.18 (m, 2H), 2.48 (m, 3H), 2.32 (s, 3H), 2.29 (m, 1H), 2.25 (m, 2H), 1.73 (m, 2H), 1.62 (m, 2H), 1.30 (d, J = 6.8 Hz, 3H).

Compound 3, Methyl 4-[[3-[1-(4-Bromophenyl)ethylureido]propyl](1,2,3,4-tetrahydro-1-naphthyl)amino]butylate, can be obtained in an analogous manner to that described for compound 27 and contains the following characteristics: MS(ES^+) m/e 530 $[M+H]^+$; ^1H NMR (400 MHz, DMSO-*d6*) δ 7.56 (d, J = 7.3 Hz, 1H), 7.48 (dd, J = 8.3, 1.2 Hz, 2H), 7.22 (d, J = 8.5 Hz, 2H), 7.06 (m, 3H), 6.26 (m, 1H), 5.71 (m, 1H), 4.67 (m, 1H), 3.85 (m, 1H), 3.54 (s, 3H), 3.00 (m, 1H), 2.91 (m, 1H), 2.67 (m, 2H), 2.34 (m, 6H), 1.92 (m, 2H), 1.64 (m, 3H), 1.49 (m, 3H), 1.27 (d, J = 7.1 Hz, 3H).

Compound 19, Methyl 4-[[3-(2-chlorobenzylureido)propyl][1-(4-chlorophenyl)ethyl]amino]butylate, can be obtained in an analogous manner to that described for compound 27 and contains the following characteristics: MS(ES$^+$) m/e 480 $[M+H]^+$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (dd, J = 7.3, 2.0 Hz, 1H), 7.34 (dd, J = 7.3, 2.0 Hz, 1H), 7.26 (m, 3H), 7.21 (m, 3H), 4.95 (br, 1H), 4.43 (d, J = 6.1 Hz, 2H), 3.87 (m, 1H), 3.63 (s, 3H), 3.18 (m, 2H), 2.48 (m, 3H), 2.35 (m, 1H), 2.25 (m, 2H), 1.74 (m, 2H), 1.62 (m, 2H), 1.30 (d, J = 6.6 Hz, 3H).

Compound 20, Methyl 4-[[3-(3-methylbenzylureido)propyl][1-(4-chlorophenyl)ethyl]amino]butylate, can be obtained in an analogous manner to that described for compound 27 and contains the following characteristics: MS(ES$^+$) m/e 460 $[M+H]^+$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 (s, 1H), 7.20 (m, 3H), 7.07 (m, 4H), 4.75 (br, 1H), 4.30 (d, J = 5.6 Hz, 2H), 3.85 (m, 1H), 3.61 (s, 3H), 3.17 (m, 2H), 2.47 (m, 3H), 2.33 (s, 3H), 2.31 (m, 1H), 2.25 (m, 2H), 1.73 (m, 2H), 1.61 (m, 2H), 1.29 (d, J = 6.6 Hz, 3H).

Compound 21, Methyl 4-[[3-(4-methylbenzylureido)propyl][1-(4-chlorophenyl)ethyl]amino]butylate, can be obtained in an analogous manner to that described for compound 27 and contains the following characteristics: MS(ES$^+$) m/e 460 $[M+H]^+$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 (m, 4H), 7.17 (d, J = 8.1 Hz, 2H), 7.12 (d, J = 7.8 Hz, 2H), 4.73 (br, 1H), 4.28 (d, J = 5.6 Hz, 2H), 3.85 (q, J = 6.8 Hz, 1H), 3.61 (s, 3H), 3.17 (m, 2H), 2.46 (m, 3H), 2.34 (m, 1H), 2.32 (s, 3H), 2.25 (m, 2H), 1.72 (m, 2H), 1.60 (m, 2H), 1.29 (d, J = 6.8 Hz, 3H).

Compound 22, Methyl 4-[[3-(3,4-dichlorobenzylureido)propyl][1-(4-chlorophenyl)ethyl]amino]butylate, can be obtained in an analogous manner to that described for compound 27 and contains the following characteristics: MS(ES$^+$) m/e 513 $[M+H]^+$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (m, 2H), 7.26 (m, 4H), 7.12 (m, 1H), 5.03 (br, 1H), 4.29 (d, J = 6.1 Hz, 2H), 3.89 (m, 1H), 3.63 (s, 3H), 3.18 (m, 2H), 2.49 (m, 3H), 2.35 (m, 1H), 2.27 (m, 2H), 1.75 (m, 2H), 1.62 (m, 2H), 1.31 (d, J = 6.8 Hz, 3H).

Compound 23, Methyl 4-[[3-(4-methoxybenzylureido)propyl][1-(4-chlorophenyl)ethyl]amino]butylate, can be obtained in an analogous manner to that described for compound 27 and contains the following characteristics: MS(ES$^+$) m/e 476 $[M+H]^+$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 (m, 4H), 7.21 (d, J = 8.5 Hz, 2H), 6.84 (d, J = 8.5 Hz, 2H), 4.75 (br, 1H), 4.26 (d, J = 5.6 Hz, 2H), 3.86 (m, 1H), 3.79 (s, 3H), 3.61 (s, 3H), 3.16 (m, 2H), 2.47 (m, 3H), 2.35 (m, 1H), 2.25 (m, 2H), 1.73 (m, 2H), 1.60 (m, 2H), 1.29 (d, J = 6.8 Hz, 3H).

Compound 24, Methyl 4-[[3-(4-bromobenzylureido)propyl][1-(4-chlorophenyl)ethyl]amino]butylate, can be obtained in an analogous manner to that described for compound 27 and contains the following characteristics: MS(ES$^+$) m/e 525 $[M+H]^+$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (d, J = 8.3 Hz, 2H), 7.26 (m, 4H), 7.17 (d, J = 8.3 Hz, 2H), 4.85 (br, 1H), 4.29 (d, J = 5.9 Hz, 2H), 3.89 (m, 1H), 3.62 (s, 3H), 3.19 (m, 2H), 2.50 (m, 3H), 2.36 (m, 1H), 2.26 (m, 2H), 1.75 (m, 2H), 1.63 (m, 2H), 1.31 (d, J = 6.6 Hz, 3H).

Compound 25, Methyl 4-[[3-(benzylureido)propyl][1-(4-chlorophenyl)ethyl]amino]butylate, can be obtained in an analogous manner to that described for compound 27 and contains the following characteristics: MS(ES$^+$) m/e 446 $[M+Na]^+$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (m, 3H), 7.25 (m, 6H), 4.82 (br, 1H), 4.34 (d, J = 5.9 Hz, 2H), 3.86 (m, 1H), 3.61 (s, 3H), 3.18 (m, 2H), 2.48 (m, 3H), 2.35 (m, 1H), 2.25 (m, 2H), 1.73 (m, 2H), 1.61 (m, 2H), 1.30 (d, J = 6.8 Hz, 3H).

Compound 26, Methyl 4-[[3-(2,4-dichlorobenzylureido)propyl][1-(4-chlorophenyl)ethyl]amino]butylate, can be obtained in an analogous manner to that described for compound 27 and contains the following characteristics: MS(ES$^+$) m/e 536 $[M+Na]^+$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 (m, 2H), 7.26 (m, 4H), 7.20 (m, 1H), 4.95 (br, 1H), 4.39 (d, J = 6.1 Hz, 2H), 3.88 (m, 1H), 3.64 (s, 3H), 3.17 (m, 2H), 2.48 (m, 3H), 2.35 (m, 1H), 2.26 (m, 2H), 1.75 (m, 2H), 1.61 (m, 2H), 1.30 (d, J = 6.8 Hz, 3H).

Compound 29, Methyl 4-[[3-(2-chlorobenzylureido)propyl][1-(4-fluorophenyl)ethyl]amino]butylate, can be obtained in an analogous manner to that described for compound 27 and contains the following characteristics: MS(ES^+) m/e 486 $[M+Na]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ 7.40 (m, 1H), 7.33 (m, 1H), 7.26 (m, 2H), 7.20 (m, 2H), 6.97 (m, 2H), 5.04 (br, 1H), 4.42 (d, J = 6.1 Hz, 2H), 3.85 (q, J = 6.8 Hz, 1H), 3.62 (s, 3H), 3.16 (m, 2H), 2.45 (m, 3H), 2.32 (m, 1H), 2.24 (m, 2H), 1.72 (m, 2H), 1.59 (m, 2H), 1.28 (d, J = 6.8 Hz, 3H).

Example 4. Synthesis of 5-[[3-(2,4-Dichlorobenzylureido)propyl][1-(4-chlorophenyl)ethyl]amino]pentanoic acid (Compound 47)

The following synthesis is depicted in Scheme 4.

To a solution of Methyl 5-[[3-(2,4-dichlorobenzylureido)propyl][1-(4-chlorophenyl)ethyl]amino]pentanoate (Compound 44, 50 mg, 0.095 mmol) in 10% water/methanol (2 ml) was added lithium hydroxide monohydrate (30 mg, 0.71 mmol). After stirring at RT for 16 h, the reaction mixture was concentrated under vacuum to dryness. After adding 1N-HCl, the mixture was extracted with chloroform, washed with brine, dried over sodium sulfate, and filtered. The filtrate was concentrated under vacuum to dryness. The residue was adsorbed on a plate of silica gel and the plate was developed with 17% methanol/chloroform to afford 5-[[3-(2,4-dichlorobenzylureido)propyl][1-(4-chlorophenyl)ethyl]amino]pentanoic acid (17 mg, 35%): MS(ES^+) m/e 514 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ 7.32 (bs, 4H), 7.29 (m, 2H), 7.15 (m, 1H), 6.32 (br, 1H), 4.34 (bs, 2H), 4.06 (q, J = 6.8 Hz, 1H), 3.14 (m, 2H), 2.71 (m, 1H), 2.64 (m, 2H), 2.52 (m, 1H), 2.22 (m, 2H), 1.73 (m, 2H), 1.52 (m, 2H), 1.44 (d, J = 6.8 Hz, 3H).

Example 5. Synthesis of N-(3,4-Dichlorophenylcarbamoyl)-N'-[2-(4-chlorophenyl)ethyl]-N'-[2-(2-methoxyethoxy)ethyl]-1,3-diaminopropane (Compound 53)

The following synthesis is depicted in Scheme 5.

Step 1: To a mixture of 2-(4-chlorophenyl)ethylamine (1.56 g, 10 mmol) and potassium carbonate (2.8 g, 20 mmol) in CH_3CN (50 ml) was added N-(3-

bromopropyl)phthalimide (3.0 g, 11 mmol). The mixture was refluxed under stirring for 16 h, and then filtered. The filtrate was concentrated under vacuum to dryness, and the residue was chromatographed on silica gel (eluting with 2.5% methanol/chloroform) to afford N-[3-[2-(4-chlorophenyl)ethylamino]propyl]phthalimide (2.28 g, 67%): MS(FD) m/e 343 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ 7.84 (m, 2H), 7.71 (m, 2H), 7.24 (d, J = 8.3 Hz, 2H), 7.11 (d, J = 8.3 Hz, 2H), 3.74 (d, J = 6.8 Hz, 2H), 2.82 (t, J = 6.8 Hz, 2H), 2.73 (t, J = 6.8 Hz, 2H), 2.66 (t, J = 6.8 Hz, 2H), 1.84 (m, 2H).

Step 2: To a mixture of N-[3-[2-(4-chlorophenyl)ethylamino]propyl]phthalimide (244 mg, 0.712 mmol) and potassium carbonate (148 mg, 1.07 mmol) in CH_3CN (4 ml) was added 1-bromo-2-(2-methoxyethoxy)ethane (195 mg, 1.07 mmol). The mixture was refluxed under stirring for 13 h, and then filtered. The filtrate was concentrated under vacuum to dryness, and the residue was adsorbed on a plate of silica gel and the plate was developed with 3% methanol/chloroform to afford N-[3-[[2-(4-chlorophenyl)ethyl] [2-(2-methoxyethoxy)ethyl]amino]propyl]phthalimide (158 mg, 50%): MS(ES^+) m/e 445 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ 7.84 (m, 2H), 7.71 (m, 2H), 7.22 (d, J = 8.3 Hz, 2H), 7.11 (d, J = 8.3 Hz, 2H), 3.70 (m, 2H), 3.58 (m, 2H), 3.53 (m, 4H), 3.37 (s, 3H), 2.71 (m, 6H), 2.62 (m, 2H), 1.83 (m, 2H).

Step 3: To a solution of N-[3-[[2-(4-chlorophenyl)ethyl] [2-(2-methoxyethoxy)ethyl]amino]propyl]phthalimide (70 mg, 0.16 mmol) in ethanol (3 ml) was added hydrazine monohydrate (53 µl, 1.1 mmol). The solution was stirred at RT for 21 h, and then filtered. The filtrate was concentrated under vacuum to dryness. After adding water, the mixture was extracted with chloroform, washed with brine, dried over sodium sulfate, and filtered. The filtrate was concentrated under vacuum to dryness. After adding chloroform (2 ml) to the residue, 3,4-dichlorophenyl isocyanate (44 mg, 0.24 mmol) was added, and the mixture was stirred at RT for 1.5 h. The reaction mixture was filtered, and the filtrate was concentrated under vacuum to dryness. The residue was adsorbed on a plate of silica

gel and then developed with 5% methanol/chloroform to afford N-(3,4-dichlorophenylcarbamoyl)-N'-[2-(4-chlorophenyl)ethyl]-N'-[2-(2-methoxyethoxy)ethyl]-1,3-diaminopropane (50 mg, 63%): MS(ES^+) m/e 502 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ 7.64 (d, J = 2.4 Hz, 1H), 7.61 (br, 1H), 7.30 (dd, J = 8.8, 2.4 Hz, 1H), 7.25 (m, 3H), 7.11 (d, J = 8.3 Hz, 2H), 6.35 (br, 1H), 3.63 (m, 6H), 3.36 (s, 3H), 3.27 (m, 2H), 2.75 (m, 6H), 2.70 (m, 2H), 1.71 (m, 2H).

Compound 48, N-(4-Cyanophenylcarbamoyl)-N'-[2-(2,4-dichlorophenyl)ethyl]-N'-[2-(2-methoxyethoxy)ethyl]-1,3-diaminopropane, can be obtained in an analogous manner to that described for compound 53 and contains the following characteristics: MS(ES^+) m/e 493 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ 8.19 (br, 1H), 7.53 (m, 5H), 7.34 (d, J = 6.3 Hz, 1H), 7.15 (s, 1H), 6.42 (br, 1H), 3.65 (m, 6H), 3.36 (s, 3H), 3.28 (m, 2H), 2.86 (m, 2H), 2.76 (m, 4H), 2.67 (m, 2H), 1.71 (m, 2H).

Compound 49, N-(4-Methoxyphenylcarbamoyl)-N'-[2-(3-chlorophenyl)ethyl]-N'-[2-(2-methoxyethoxy)ethyl]-1,3-diaminopropane, can be obtained in an analogous manner to that described for compound 53 and contains the following characteristics: MS(ES^+) m/e 464 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ 7.28 (d, J = 9.0 Hz, 2H), 7.18 (m, 3H), 7.05 (m, 1H), 6.95 (br, 1H), 6.81 (d, J = 9.0 Hz, 2H), 5.94 (br, 1H), 3.76 (s, 3H), 3.63 (m, 2H), 3.59 (m, 4H), 3.35 (s, 3H), 3.26 (m, 2H), 2.69 (m, 6H), 2.61 (m, 2H), 1.66 (m, 2H).

Compound 50, N-(4-Cyanophenylcarbamoyl)-N'-[2-(3-chlorophenyl)ethyl]-N'-[2-(2-methoxyethoxy)ethyl]-1,3-diaminopropane, can be obtained in an analogous manner to that described for compound 53 and contains the following characteristics: MS(ES^+) m/e 459 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ 7.85 (br, 1H), 7.55 (m, 2H), 7.50 (m, 2H), 7.17 (m, 3H), 7.05 (m, 1H), 6.42 (br, 1H), 3.65 (m, 6H), 3.36 (s, 3H), 3.24 (m, 2H), 2.71 (m, 6H), 2.62 (t, J = 5.9 Hz, 2H), 1.69 (m, 2H).

Compound 51, N-(3,4-Dichlorophenylcarbamoyl)-N'-[2-(3-chlorophenyl)ethyl]-N'-[2-(2-methoxyethoxy)ethyl]-1,3-diaminopropane, can be obtained in an analogous manner to that described for compound 53 and contains the following characteristics: MS(ES$^+$) m/e 502 $[M+H]^+$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 (d, J = 2.4 Hz, 1H), 7.56 (br, 1H), 7.31 (dd, J = 8.8, 2.4 Hz, 1H), 7.25 (d, J = 8.8 Hz, 1H), 7.18 (m, 3H), 7.06 (m, 1H), 6.35 (br, 1H), 3.65 (m, 6H), 3.36 (s, 3H), 3.24 (m, 2H), 2.71 (m, 6H), 2.63 (t, J = 5.9 Hz, 2H), 1.68 (m, 2H).

Compound 52, N-(3,4-Dichlorophenylcarbamoyl)-N'-[2-(2,4-dichlorophenyl)ethyl]-N'-[2-(2-methoxyethoxy)ethyl]-1,3-diaminopropane, can be obtained in an analogous manner to that described for compound 53 and contains the following characteristics: MS(ES$^+$) m/e 536 $[M+H]^+$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (d, J = 2.4 Hz, 1H), 7.36 (s, 1H), 7.31 (dd, J = 8.8, 2.4 Hz, 1H), 7.25 (m, 1H), 7.15 (m, 2H), 6.35 (br, 1H), 3.66 (m, 6H), 3.36 (s, 3H), 3.30 (m, 2H), 2.86 (m, 2H), 2.71 (m, 6H), 1.72 (m, 2H).

Compound 54, N-(4-Cyanophenylcarbamoyl)-N'-[2-(3,4-dichlorophenyl)ethyl]-N'-[2-(2-methoxyethoxy)ethyl]-1,3-diaminopropane, can be obtained in an analogous manner to that described for compound 53 and contains the following characteristics: MS(ES$^+$) m/e 493 $[M+H]^+$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (br, 1H), 7.55 (d, J = 8.8 Hz, 2H), 7.50 (d, J = 9.0 Hz, 2H), 7.33 (d, J = 8.0 Hz, 1H), 7.27 (m, 1H), 7.01 (dd, J = 8.3, 2.0 Hz, 1H), 6.40 (br, 1H), 3.65 (m, 6H), 3.36 (s, 3H), 3.26 (m, 2H), 2.73 (m, 6H), 2.64 (t, J = 5.9 Hz, 2H), 1.71 (m, 2H).

Compound 55, N-(Phenylcarbamoyl)-N'-[2-(3-chlorophenyl)ethyl]-N'-[2-(2-methoxyethoxy)ethyl]-1,3-diaminopropane, can be obtained in an analogous manner to that described for compound 53 and contains the following characteristics: MS(ES$^+$) m/e 434 $[M+H]^+$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (dd, J = 8.5, 1.0 Hz, 2H), 7.28 (br, 1H), 7.23 (m, 2H), 7.17 (m, 3H), 7.05 (m, 1H), 6.95 (m, 1H), 6.10 (br, 1H), 3.63 (m, 6H), 3.36 (s, 3H), 3.26 (m, 2H), 2.71 (m, 6H), 2.61 (t, J = 6.1 Hz, 2H), 1.66 (m, 2H).

Compound 56, N-(3,4-Dichlorophenylcarbamoyl)-N'-(2-phenylethyl)-N'-[2-(2-methoxyethoxy)ethyl]-1,3-diaminopropane, can be obtained in an analogous manner to that described for compound 53 and contains the following characteristics: MS(ES^+) m/e 468 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ 7.63 (d, J = 2.4 Hz, 1H), 7.49 (br, 1H), 7.30 (m, 1H), 7.25 (m, 3H), 7.18 (m, 3H), 6.38 (br, 1H), 3.63 (m, 6H), 3.35 (s, 3H), 3.26 (m, 2H), 2.74 (m, 4H), 2.70 (m, 2H), 2.63 (m, 2H), 1.68 (m, 2H).

Compound 57, N-(Phenylcarbamoyl)-N'-[2-(3-methoxyphenyl)ethyl]-N'-[2-(2-methoxyethoxy)ethyl]-1,3-diaminopropane, can be obtained in an analogous manner to that described for compound 53 and contains the following characteristics: MS(ES^+) m/e 430 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ 7.40 (dd, J = 8.5, 1.0 Hz, 2H), 7.21 (m, 4H), 6.95 (t, J = 7.3 Hz, 1H), 6.77 (d, J = 7.6 Hz, 1H), 6.73 (m, 2H), 6.18 (br, 1H), 3.77 (s, 3H), 3.62 (m, 6H), 3.35 (s, 3H), 3.29 (t, J = 5.6 Hz, 2H), 2.73 (bs, 4H), 2.70 (m, 2H), 2.63 (m, 2H), 1.68 (m, 2H).

Compound 58, N-(Phenylcarbamoyl)-N'-[1-(4-chlorophenyl)ethyl]-N'-[2-(2-methoxyethoxy)ethyl]-1,3-diaminopropane, can be obtained in an analogous manner to that described for compound 53 and contains the following characteristics: MS(ES^-) m/e 432 $[M-H]^-$; ^1H NMR (400 MHz, $CDCl_3$) δ 7.53 (m, 1H), 7.41 (m, 2H), 7.33 (m, 2H), 7.26 (m, 4H), 6.95 (t, J = 6.3 Hz, 1H), 6.17 (br, 1H), 4.00 (q, J = 6.8 Hz, 1H), 3.69-3.45 (m, 7H), 3.19 (m, 1H), 2.60 (m, 3H), 2.55 (m, 1H), 1.67 (m, 2H), 1.32 (d, J = 6.8 Hz, 3H).

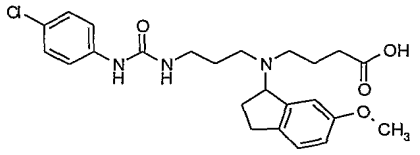
Compound 59, N-(4-Bromophenylcarbamoyl)-N'-[1-(4-chlorophenyl)ethyl]-N'-[2-(2-methoxyethoxy)ethyl]-1,3-diaminopropane, can be obtained in an analogous manner to that described for compound 53 and contains the following characteristics: MS(ES^-) m/e 510 $[M-H]^-$; ^1H NMR (400 MHz, $CDCl_3$) δ 7.53 (br, 1H), 7.33 (m, 4H), 7.27 (m, 4H), 6.33 (br, 1H), 4.03 (m, 1H), 3.75-3.48 (m, 7H), 3.37 (s, 3H), 3.16 (m, 1H), 2.62 (m, 3H), 2.55 (m, 1H), 1.68 (m, 2H), 1.33 (d, J = 6.8 Hz, 3H).

Compound 60, N-(Phenylcarbamoyl)-N'-[2-(2-chlorophenyl)ethyl]-N'-[2-(2-methoxyethoxy)ethyl]-1,3-diaminopropane, can be obtained in an analogous manner to that described for compound 53 and contains the following characteristics: MS(ES^+) m/e 456 $[M+Na]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ 7.41 (d, J = 7.6 Hz, 2H), 7.33 (m, 1H), 7.29 (br, 1H), 7.22 (m, 3H), 7.15 (m, 2H), 6.94 (m, 1H), 6.25 (br, 1H), 3.66 (m, 6H), 3.36 (s, 3H), 3.30 (m, 2H), 2.88 (m, 2H), 2.75 (m, 4H), 2.67 (m, 2H), 1.70 (m, 2H).

Compound 61, N-(Phenylcarbamoyl)-N'-[2-(4-bromophenyl)ethyl]-N'-[2-(2-methoxyethoxy)ethyl]-1,3-diaminopropane, can be obtained in an analogous manner to that described for compound 53 and contains the following characteristics: MS(ES^+) m/e 500 $[M+Na]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ 7.39 (m, 4H), 7.29 (br, 1H), 7.23 (m, 2H), 7.05 (d, J = 8.3 Hz, 2H), 6.95 (m, 1H), 3.61 (m, 6H), 3.36 (s, 3H), 3.27 (t, J = 5.6 Hz, 2H), 2.69 (m, 6H), 2.62 (m, 2H), 1.68 (m, 2H).

Compound 62, N-(Phenylcarbamoyl)-N'-[2-(4-fluorophenyl)ethyl]-N'-[2-(2-methoxyethoxy)ethyl]-1,3-diaminopropane, can be obtained in an analogous manner to that described for compound 53 and contains the following characteristics: MS(ES^+) m/e 440 $[M+Na]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ 7.40 (dd, J = 8.5, 1.0 Hz, 2H), 7.28 (br, 1H), 7.23 (m, 2H), 7.13 (m, 2H), 6.95 (m, 3H), 3.63 (m, 6H), 3.37 (s, 3H), 3.27 (m, 2H), 2.70 (m, 6H), 2.63 (m, 2H), 1.68 (m, 2H).

Example 6. Synthesis of 4-[[3-[(4-Chloroanilino)carbonylamino]propyl](6-methoxy -1-indanyl)amino]butanoic acid (Compound 63):



The following synthesis is depicted in Scheme 6.

Step 1: To a solution of 6-methoxy-1-indanone (5.0 g, 30 mmol) in EtOH (20 ml) was added sodium borohydride (3.5g, 93 mmol) at 0 °C, and the mixture was stirred at 0 °C for 3 h. The solution was concentrated under vacuum to dryness. After adding water, the mixture was extracted with chloroform, dried over sodium

sulfate, and filtered. The filtrate was concentrated under vacuum to dryness, and the residue was chromatographed on silica gel (eluting with 30% ethyl acetate/hexane) to afford 6-methoxy-1-indanol (5.0 g, 99%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.03 (d, J = 8.0 Hz, 1H), 6.84 (s, 1H), 6.71 (d, J = 8.0 Hz, 1H), 5.07 (t, J = 6.0 Hz 1H), 2.86 (m, 1H), 2.64 (m, 1H), 2.39 (m, 1H), 1.82 (m, 1H).

Step 2: To a solution of 6-methoxy-1-indanol (4.6 g, 28 mmol) in toluen(50 ml) were added iminodicarboxylic acid di-*tert*-butyl ester (9.2 g, 42 mmol) and tri-*n*-butylphosphine (8.6 g, 42 mmol), and the mixture was cooled to 0 °C. After adding 1,1'-(azodicarbonyl)dipiperidine, the solution was stirred at RT for 3 h, and then filtered. The filtrate was concentrated under vaccum to dryness, and the residue was chromatographed on silica gel (eluting with 4% ethyl acetate/hexane) to afford *tert*-butyl [(*tert*-butoxycarbonyl)(6-methoxy-1-indanyl)amino]methanoate (8.5 g, 83%): MS(ES$^+$) m/e 386 $[M+Na]^+$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.00 (d, J = 8.0 Hz, 1H), 6.68 (d, J = 8.0 Hz, 1H), 6.64 (s, 3H), 5.70 (t, J = 8.4 Hz, 1H), 3.68 (s, 3H), 2.90 (m, 1H), 2.72 (m, 1H), 2.40 (m, 1H), 2.25 (m, 1H), 1.29 (m, 18H).

Step 3: *tert*-Butyl[(*tert*-butoxycarbonyl)(6-methoxy -1-indanyl)amino]methanoate (8.5g, 23 mmol) in 40% TFA/CH_2Cl_2 was stirred at RT for 2h. After neutralized with 50% NaOH*aq*. the mixture was extracted with chloroform, dried over sodium sulfate, and filtered. Concentrating under vacuum gave 1-amino-6-methoxyindan (1.9g, 50%) which was used in the next step without further purification.

Step 4: To a mixture of 1-amino-6-methoxyindan (1.9 g, 12 mmol) and potassium carbonate (5.0 g, 36 mmol) in CH_3CN (50 ml) was added N-(3-Bromopropyl)phthalimide (3.9 g, 14 mmol). The mixture was refluxed under stirring for 18 h, and then filtered. The filtrate was concentrated under vacuum to dryness, and the residue was chromatographed on silica gel (eluting with 2.5% methanol/chloroform) to afford 2-[3-[(6-methoxy -1-indanyl)amino]propyl]-1,3-isoindolinedione (2.5 g, 60%): MS(ES$^+$) m/e 351 $[M+H]^+$; ^{1}H NMR (400 MHz,

$CDCl_3$) δ 7.75 (m, 2H), 7.63 (m, 2H), 7.05 (d, J = 4.0 Hz, 1H), 6.81 (s, 1H), 6.65 (d, J = 4.0 Hz, 2H), 4.09 (t, J = 6.8 Hz, 1H), 3.72 (m, 5H), 2.72-2.52 (m, 4H), 2.29 (m, 1H)), 1.84-1.71 (m, 3H).

Step 5: To a solution of 2-[3-[(6-methoxy -1-indanyl)amino]propyl]-1,3-isoindolinedione (2.4 g, 7.0 mmol) in 20% EtOH/DMF (30 ml) were added succinic semialdehyde (15 wt.% solution in water, 12 ml, 17 mmol) and BAP (3.6 ml, 35 mmol), and the mixture was stirred at RT for 18 h. After adding water, the mixture was extracted with chloroform, washed with water and brine, dried over sodium sulfate, and filtered. The filtrate was concentrated under vacuum to dryness, and the residue was chromatographed on silica gel (eluting with 5% methanol/chloroform) to afford 4-[[3-(1,3-dioxo-2-isoindolyl)propyl](6-methoxy -1-indanyl)amino]butanoic acid (1.3 g, 43%): MS(ES^+) m/e 437 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ 7.81 (m, 2H), 7.71 (m, 2H), 7.05 (m, 2H), 6.75 (d, J = 8.4 Hz, 1H), 4.68 (t, J = 6.8 Hz 1H), 3.73-3.63 (m, 5H), 2.91-2.74 (m, 3H), 2.62-2.50 (m, 4H), 2.29-2.15 (m, 2H), 2.14-2.01 (m, 3H), 1.96-1.87 (m, 1H).

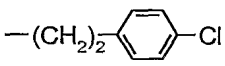
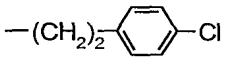
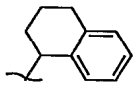
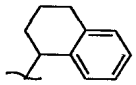
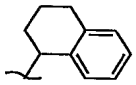
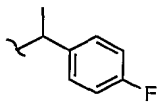
Step 6: To a solution of 4-[[3-(1,3-dioxo-2-isoindolyl)propyl](6-methoxy -1-indanyl)amino]butanoic acid (1.3 g, 3.3 mmol) in EtOH (50 ml) was added hydrazine monohydrate (0.35 ml, 8.5 mmol), and the mixture was stirred at RT for 6 h. After adding chloroform (50 ml) and MeOH (25 ml), the reaction mixture was filtered, and the filtrate was concentrated under vacuum to dryness. After adding DMF (30 ml) to the residue, 4-chlorophenyl isocyanate (1.5 g, 9.7 mmol) was added, and the mixture was stirred at RT for 18 h. After adding water, the mixture was extracted with chloroform, dried over sodium sulfate, and filtered. The filtrate was concentrated under vacuum to dryness. The residue was chromatographed on silica gel (eluting with 17% methanol/chloroform) to afford 4-[[3-[(4-chloroanilino)carbonylamino]propyl](6-methoxy-1-indanyl)amino]butanoic acid (520 mg, 34%): MS(ES^-) m/e 458 $[M-H]^-$; ^1H NMR (400 MHz, $CDCl_3$) δ 9.20(bs, 1H), 7.43-7.12 (m, 6H), 7.87 (m, 1H), 4.90 (t, J = 6.8 Hz, 1H), 4.69 (s, 3H), 3.38-2.84 (m, 8H), 2.55-2.01(m, 7H), 1.80 (m, 1H).

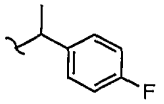
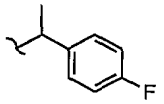
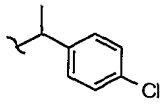
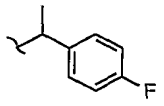
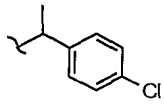
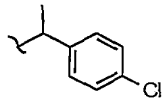
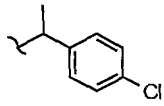
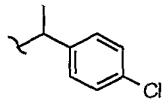
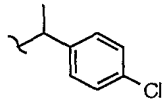
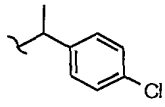
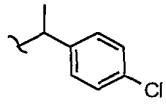
Abbreviations:

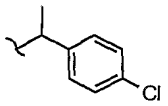
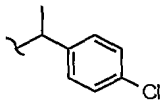
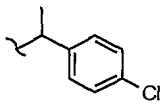
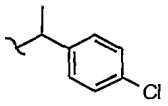
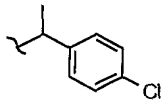
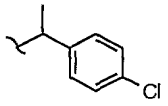
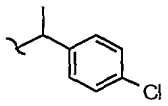
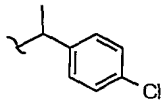
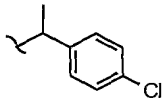
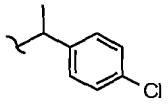
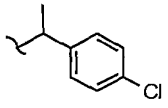
EtOH	ethanol
MeOH	methanol
DMF	N,N-dimethylformamide
BAP	borane and pyridine
TFA	trifluoroacetic acid

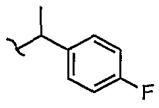
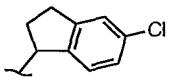
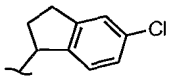
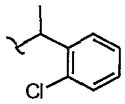
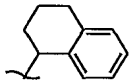
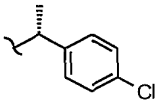
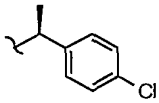
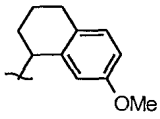
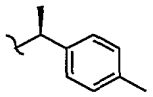
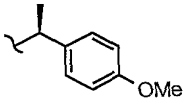
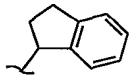
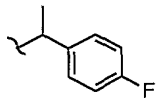
Tables 1a, 1b, and 1c list a variety of compounds that can be synthesized by using one of the methods described above.

Table 1A

CPD No.	Ar	R11,R12	m	R1	R2	Mass Spec. m/e		
1	Phenyl	H,H	3		ethyl	ES$^-$	408	[M-H]$^-$
2	Phenyl	H,H	2		ethyl	ES$^-$	394	[M-H]$^-$
3	4-bromophenyl	Me,H	3		-(CH$_2$)$_3$CO$_2$Me	ES$^+$	530	M+H]$^+$
4	4-bromophenyl	Me,H	3		-(CH$_2$)$_3$CO$_2$H	ES$^-$	514	[M-H]$^-$
5	2,5-dichloro phenyl	H,H	3		-(CH$_2$)$_3$CO$_2$H	ES$^+$	492	M+H]$^+$
6	4-fluorophenyl	H,H	3		-(CH$_2$)$_3$CH$_3$	ES$^+$	404	M+H]$^+$

7	2-chlorophenyl	H,H	3		-$(CH_2)_3CH_3$	ES^+	420	$M+H]^+$
8	phenyl	H,H	3		-$(CH_2)_3CH_3$	ES^+	386	$M+H]^+$
9	2-chlorophenyl	H,H	3		-$(CH_2)_3CH_3$	ES^+	436	$M+H]^+$
10	2-chlorophenyl	H,H	3		-$(CH_2)_3CO_2H$	ES^+	450	$M+H]^+$
11	2-chlorophenyl	H,H	3		-$(CH_2)_3CO_2H$	ES^+	488	M+Na]
12	2,4-dichloro phenyl	H,H	3		-$(CH_2)_3CO_2H$	ES^+	522	M+Na]
13	2-methylphenyl	H,H	3		-$(CH_2)_3CO_2H$	ES^+	468	M+Na]
14	3-methylphenyl	H,H	3		-$(CH_2)_3CO_2H$	ES^+	468	M+Na]
15	4-methylphenyl	H,H	3		-$(CH_2)_3CO_2H$	ES^+	468	M+Na]
16	3,4-dichloro phenyl	H,H	3		-$(CH_2)_3CO_2H$	ES^+	522	M+Na]
17	4-methoxyphenyl	H,H	3		-$(CH_2)_3CO_2H$	ES^+	484	M+Na]

18	4-bromophenyl	H,H	3		-$(CH_2)_3CO_2H$	ES^+	532	M+Na]
19	2-chlorophenyl	H,H	3		-$(CH_2)_3CO_2Me$	ES^+	480	$M+H]^+$
20	3-methylphenyl	H,H	3		-$(CH_2)_3CO_2Me$	ES^+	460	$M+H]^+$
21	4-methylphenyl	H,H	3		-$(CH_2)_3CO_2Me$	ES^+	460	$M+H]^+$
22	3,4-dichloro phenyl	H,H	3		-$(CH_2)_3CO_2Me$	ES^+	513	$M+H]^+$
23	4-methoxyphenyl	H,H	3		-$(CH_2)_3CO_2Me$	ES^+	476	$M+H]^+$
24	4-bromophenyl	H,H	3		-$(CH_2)_3CO_2Me$	ES^+	525	$M+H]^+$
25	Phenyl	H,H	3		-$(CH_2)_3CO_2Me$	ES^+	446	M+Na]
26	2,4-dichloro phenyl	H,H	3		-$(CH_2)_3CO_2Me$	ES^+	536	M+Na]
27	2-methylphenyl	H,H	3		-$(CH_2)_3CO_2Me$	ES^+	482	M+Na]
28	Phenyl	H,H	3		-$(CH_2)_3CO_2H$	ES^+	454	M+Na]

29	2-chlorophenyl	H,H	3		-$(CH_2)_3CO_2Me$	ES^+	486	M+Na]
30	2,4-dichloro phenyl	H,H	3		-$(CH_2)_3CO_2H$	ES^+	512	$M+H]^+$
31	2,4-dichloro phenyl	H,H	3		-$(CH_2)_3CO_2H$	ES^+	500	$M+H]^+$
32	2,4-dichloro phenyl	H,H	3		-$(CH_2)_3CO_2H$	ES^+	522	M+Na]
33	2,4-dichloro phenyl	H,H	3		-$(CH_2)_3CO_2H$	ES^+	492	$M+H]^+$
34	2,4-dichloro phenyl	H,H	3		-$(CH_2)_3CO_2H$	ES^+	500	$M+H]^+$
35	2,4-dichloro phenyl	H,H	3		-$(CH_2)_3CO_2H$	ES^+	500	$M+H]^+$
36	2,4-dichloro phenyl	H,H	3		-$(CH_2)_3CO_2H$	ES^+	522	$M+H]^+$
37	2,4-dichloro phenyl	H,H	3		-$(CH_2)_3CO_2H$	ES^+	502	M+Na]
38	2,4-dichloro phenyl	H,H	3		-$(CH_2)_3CO_2H$	ES^+	518	M+Na]
39	2,4-dichloro phenyl	H,H	3		-$(CH_2)_3CO_2H$	ES^+	478	$M+H]^+$
40	2,4-dichloro phenyl	H,H	3		-$(CH_2)_3CO_2H$	ES^+	484	$M+H]^+$

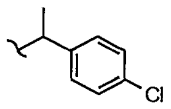
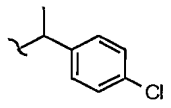
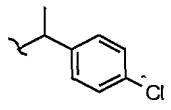
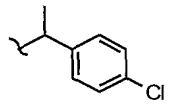
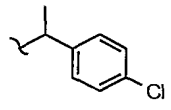
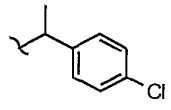
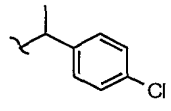
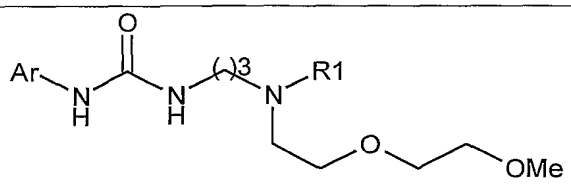
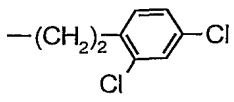
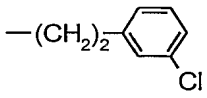
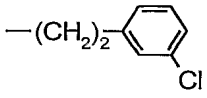
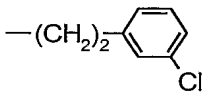
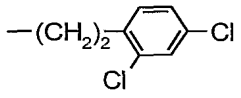
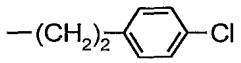
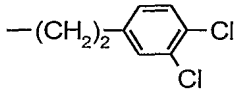
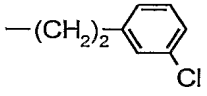
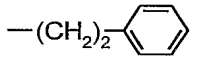
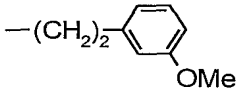
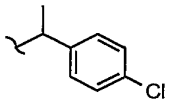
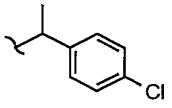
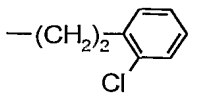
41	2,4-dichloro phenyl	H,H	3		-$(CH_2)_3CH_3$	ES^+	470	$M+H]^+$
42	2,4-dichloro phenyl	H,H	4		-$(CH_2)_3CO_2H$	ES^+	536	M+Na]
43	2,4-dichloro phenyl	H,H	5		-$(CH_2)_3CO_2H$	ES^+	550	M+Na]
44	2,4-dichloro phenyl	H,H	3		-$(CH_2)_4CO_2Me$	ES^+	550	M+Na]
45	2,4-dichloro phenyl	H,H	3		-$(CH_2)_5CO_2Et$	ES^+	578	M+Na]
46	2,4-dichloro phenyl	H,H	3		ethyl	ES^+	442	$M+H]^+$
47	2,4-dichloro phenyl	H,H	3		-$(CH_2)_4CO_2H$	ES^+	514	$M+H]^+$

Table 1B



CPD No.	Ar	R1	Mass Spec. m/e		
48	4-cyanophenyl		ES^+	493	$[M+H]^+$

49	4-methoxyphenyl		ES^+	464	$[M+H]^+$
50	4-cyanophenyl		ES^+	459	$[M+H]^+$
51	3,4-dichloro phenyl		ES^+	502	$[M+H]^+$
52	3,4-dichloro phenyl		ES^+	536	$[M+H]^+$
53	3,4-dichloro phenyl		ES^+	502	$[M+H]^+$
54	4-cyanophenyl		ES^+	493	$[M+H]^+$
55	phenyl		ES^+	434	$[M+H]^+$
56	3,4-dichloro phenyl		ES^+	468	$[M+H]^+$
57	phenyl		ES^+	430	$[M+H]^+$
58	phenyl		ES^-	432	$[M-H]^-$
59	4-bromophenyl		ES^-	510	$[M-H]^-$
60	phenyl		ES^+	456	$[M+Na]^+$

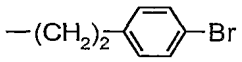
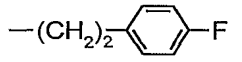
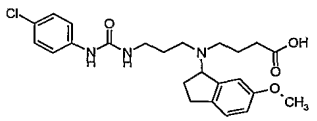
61	phenyl		ES+	500	[M+Na]+
62	phenyl		ES+	440	[M+Na]+

Table 1C

CPD No.		Mass Spec. m/e		
63		ES-	458	[M-H]-

Example 7. Synthesis of 4-[[3-[2-[4-(Benzyloxy)-3-methoxyphenyl]acetylamino]propyl][1-(4-chlorophenyl)ethyl]amino]butanoic acid (Compound 87)

The following synthesis is depicted in Scheme 7.

Step 1: N-(3-Bromopropyl)phthalimide (4.1 g, 15 mmol) was added to a mixture of 1-(4-chlorophenyl)ethylamine (2.0 g, 13 mmol) and potassium carbonate (5.3 g, 39 mmol) in CH_3CN (50 ml). The mixture was refluxed under stirring for 18 h, and then filtered. The filtrate was concentrated under vacuum to dryness, and the residue was chromatographed on silica gel (eluting with 1.5% methanol/chloroform) to afford N-[3-[1-(4-chlorophenyl)ethylamino]propyl]phthalimide (3.0 g, 68%): MS(ES^+) m/e 343 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ 7.83 (m, 2H), 7.72 (m, 2H), 7.23 (d, J = 8.0 Hz, 4H), 3.73 (m, 3H), 2.50 (m, 1H), 2.44 (m, 1H), 1.83 (m, 2H), 1.32 (d, J = 6.6 Hz, 3H).

Step 2: To a solution of N-[3-[1-(4-chlorophenyl)ethylamino]propyl]phthalimide (1.4 g, 4.1 mmol) in 20% EtOH/DMF (50 ml) were added succinic semialdehyde (15 wt.% solution in water, 5.0 ml, 8.2 mmol) and BAP (0.80 ml, 8.2 mmol), and the mixture was stirred at RT for 18 h. After adding water, the mixture was extracted with chloroform, washed with water and brine, dried over sodium sulfate, and filtered. The filtrate was concentrated under vacuum to dryness, and the residue was chromatographed on silica gel (eluting with 5% methanol/chloroform) to afford 4-[[(3-phthalimido)propyl][1-(4-chlorophenyl)ethyl]amino]butanoic acid (1.32 g, 75%): MS(ES^+) m/e 429 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ 7.84 (m, 2H), 7.75 (m, 2H), 7.26 (m, 4H), 4.05 (q, J = 6.8 Hz, 1H), 3.68 (m, 2H), 2.81 (m, 2H), 2.69 (m, 1H), 2.58 (m, 1H), 2.44 (t, J = 5.9 Hz, 2H), 2.01 (m, 2H), 1.82 (m, 2H), 1.51 (d, J = 6.8 Hz, 3H).

Step 3: To a solution of 4-[[(3-phthalimido)propyl][1-(4-chlorophenyl)ethyl]amino]butanoic acid (2.6 g, 5.3 mmol) in EtOH (10 ml) was added hydrazine monohydrate (0.7 ml, 13.3 mmol), and the mixture was stirred at RT for 6 h, and then filtered. The filtrate was concentrated under vacuum to

dryness. After adding water, the mixture was extracted with chloroform, washed with brine, dried over sodium sulfate, and filtered. Concentrating under vacuum gave 4-[(3-aminopropyl)[1-(4-chlorophenyl)ethyl]amino]butanoic acid (1.5 g, 85%) which was used in the next step without further purification.

Step 4: (4-Benzyloxy-3-methoxyphenyl)acetic acid (1.8g, 6.7 mmol) in 20% $SOCl_2/CH_2Cl_2$ was refluxed under stirring for 18h(see. Scheme 8). The reaction mixture was concentrated under vaccum to dryness. After adding 1,3-dioxane (10 ml) to the residue, 4-[(3-aminopropyl)[1-(4-chlorophenyl)ethyl]amino]butanoic acid (1.5 g, 4.5 mmol) in DMF (30 ml) was added, and the mixture was stirred at RT for 10 h. After adding water, the mixture was extracted with chloroform, dried over sodium sulfate, and filtered. The filtrate was concentrated under vacuum to dryness. The residue was chromatographed on silica gel (eluting with 17% methanol/chloroform) to afford 4-[[3-[2-[4-(benzyloxy)-3-methoxyphenyl]acetylamino]propyl][1-(4-chlorophenyl)ethyl]amino]butanoic acid (900mg, 36%) : MS(ES^+) m/e 553 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ 7.34-7.15 (m, 9H), 6.76 (m, 2H), 6.69 (m, 1H), 5.03 (s, 2H), 3.97 (q, J = 6.8 Hz, 1H), 3.79 (s, 3H), 3.36 (s, 2H), 3.13 (m, 2H), 2.56 (m, 2H), 2.44 (m, 2H), 2.24 (m, 2H), 1.71-1.51 (m, 4H), 1.33 (d, J = 6.8 Hz, 3H).

Compound 90, 4-[[3-(4-Biphenylacetylamino)propyl] [1-(4-chlorophenyl)ethyl]amino]butanoic acid, can be obtained in an analogous manner to that described for compound 87 and contains the following characteristics: MS(ES^+) m/e 493 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ 7.47-7.15 (m, 13H), 6.89 (br, 1H), 3.96 (q, J = 6.8 Hz, 3H), 3.46 (s, 2H), 3.15 (m, 2H), 2.57 (m, 2H), 2.44 (m, 2H), 2.24 (m, 2H), 1.69 (m, 2H), 1.58 (m, 2H), 1.34 (d, J = 6.8 Hz, 3H).

Compound 109, 4-[[3-[2-[4-(Benzyloxy)phenyl]acetylamino]propyl][(1*S*)-1-(4-chlorophenyl)ethyl]amino]butanoic acid, can be obtained in an analogous manner to that described for compound 87 and contains the following characteristics: MS(ES^+) m/e 524 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ 7.42-7.16 (m, 11H),

6.93 (m, 2H), 5.03 (s, 2H), 4.06 (q, J=6.8Hz 1H), 3.46 (s, 2H), 3.21 (m, 2H), 2.70-2.47 (m, 4H), 2.39-2.23 (m, 2H), 1.81-1.62 (m, 4H), 1.44 (d, J=6.8Hz, 3H).

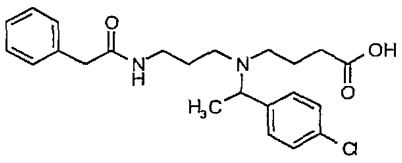
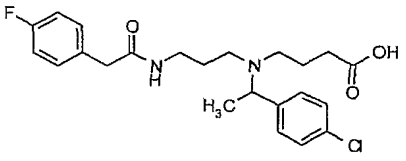
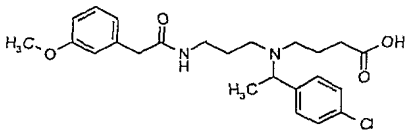
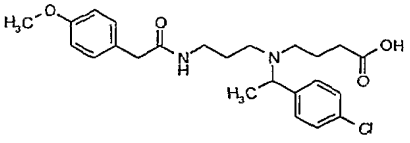
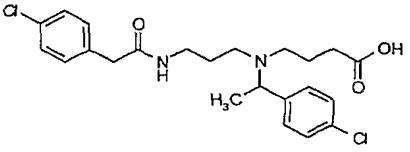
Compound 114, 4-[[3-[2-[4-(Benzyloxy)phenyl]acetylamino]propyl][(1*S*)-1-(4-bromophenyl)ethyl]amino]butanoic acid, can be obtained in an analogous manner to that described for compound 87 and contains the following characteristics: MS(ES^+) m/e 569 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ 7.42-7.15 (m, 11H), 6.92 (m, 2H), 5.03 (s, 2H), 4.08 (q, J=6.8Hz 1H), 3.44 (s, 2H), 3.21 (m, 2H), 2.74-2.52 (m, 4H), 2.40-2.25 (m, 2H), 1.85-1.60 (m, 4H), 1.47 (d, J=6.8Hz, 3H).

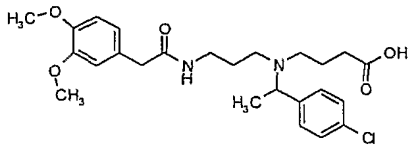
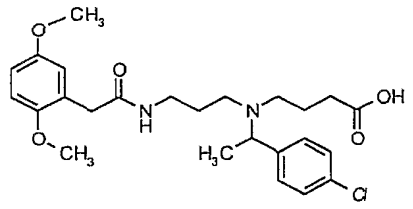
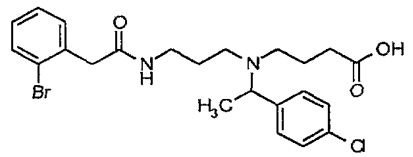
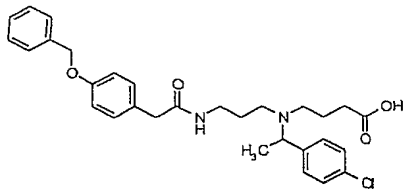
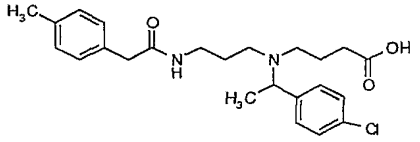
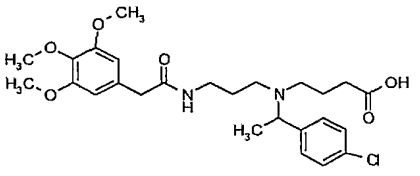
Compound 125, 4-[[3-[2-[4-(Benzyloxy)-3-methoxyphenyl]acetylamino]propyl][(1*S*)-1-(4-chlorophenyl)ethyl]amino]butanoic acid, can be obtained in an analogous manner to that described for compound 87 and contains the following characteristics: MS(ES^+) m/e 554 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ 7.42-7.22 (m, 9H), 6.84 (m, 2H), 6.72 (m, 1H), 6.61 (br, 1H), 5.10 (s, 2H), 4.02 (q, J=6.8Hz 1H), 3.86 (s, 3H), 3.43 (s, 2H), 3.20 (m, 2H), 2.67-2.28 (m, 6H), 1.78-1.64 (m, 4H), 1.40 (d, J=6.8Hz, 3H).

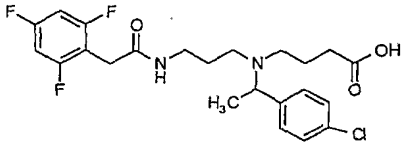
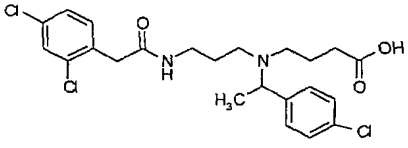
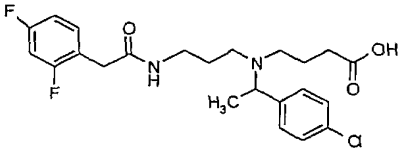
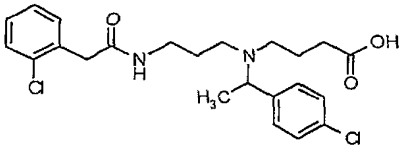
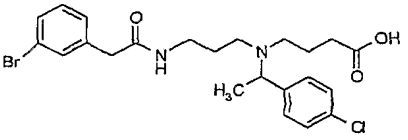
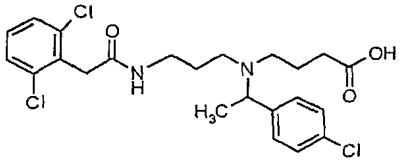
Compound 126, 4-[[3-[2-[4-(Benzyloxy)-3-methoxyphenyl]acetylamino]propyl][(1*S*)-1-(4-bromophenyl)ethyl]amino]butanoic acid, can be obtained in an analogous manner to that described for compound 87 and contains the following characteristics: MS(ES^+) m/e 599 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ 7.48-7.16 (m, 9H), 6.84 (m, 2H), 6.72 (m, 1H), 6.51 (br, 1H), 5.10 (s, 2H), 4.00 (q, J=6.8Hz 1H), 3.86 (s, 3H), 3.43 (s, 2H), 3.19 (m, 2H), 2.66-2.28 (m, 6H), 1.76-1.63 (m, 4H), 1.40 (d, J=6.8Hz, 3H).

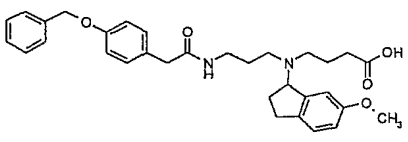
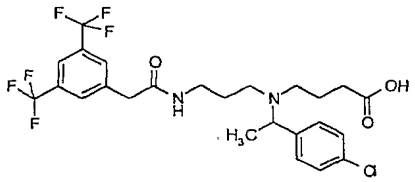
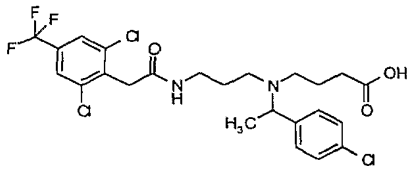
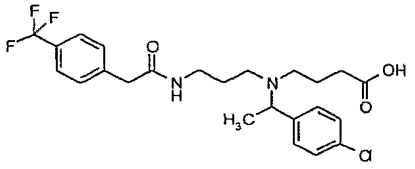
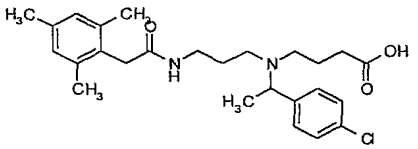
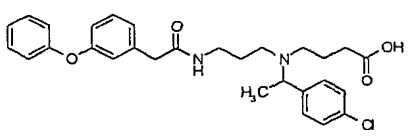
The following compounds, listed in Table 1D, were obtained in an analogous manner to those of compounds described above.

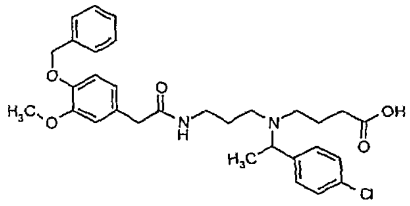
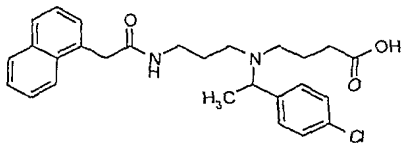
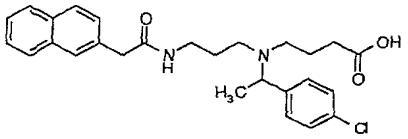
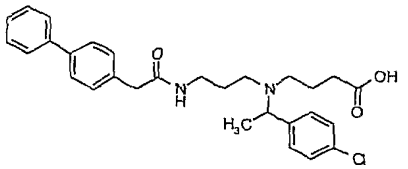
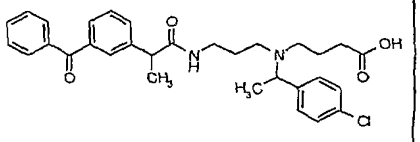
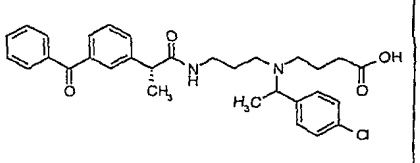
Table 1D

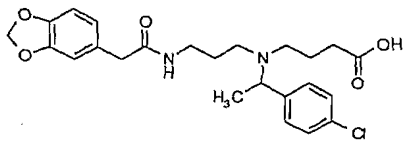
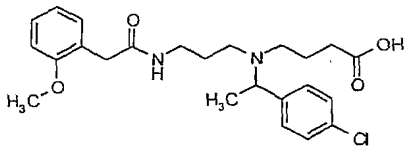
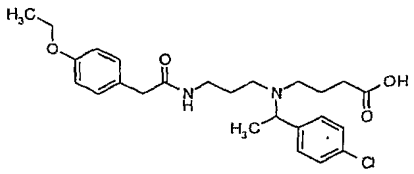
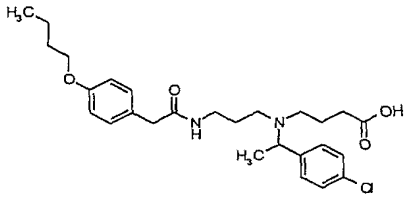
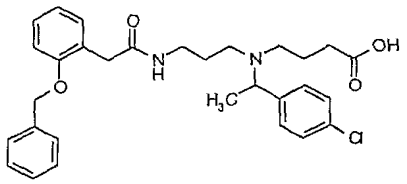
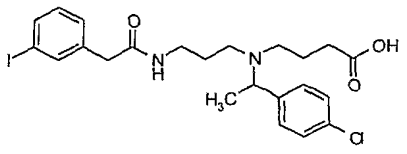
CPD No.	Structure	Mass Spec. m/e		
64		ES^+	417	$[M+H]^+$
65		ES^+	435	$[M+H]^+$
66		ES^+	447	$[M+H]^+$
67		ES^+	447	$[M+H]^+$
68		ES^+	452	$[M+H]^+$

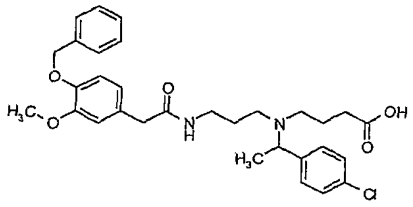
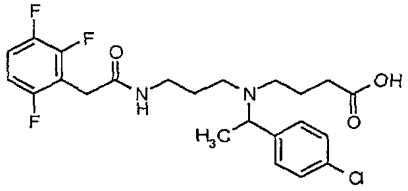
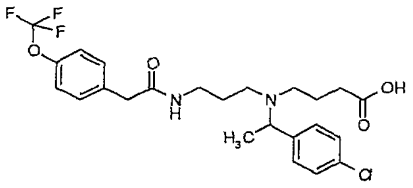
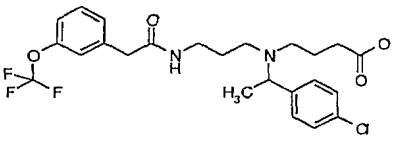
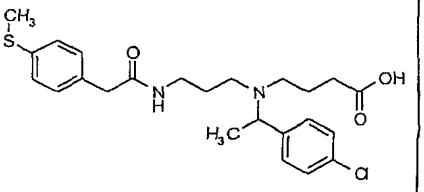
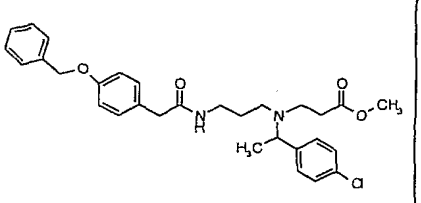
69		ES^+	477	$[M+H]^+$
70		ES^+	477	$[M+H]^+$
71		ES^+	496	$[M+H]^+$
72		ES^+	524	$[M+H]^+$
73		ES^+	431	$[M+H]^+$
74		ES^+	508	$[M+H]^+$

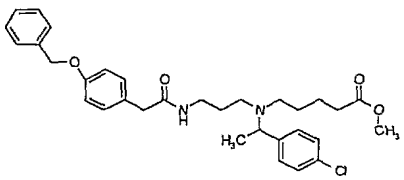
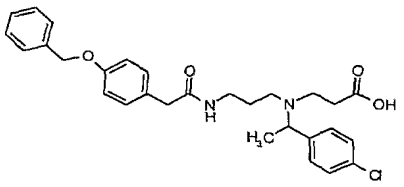
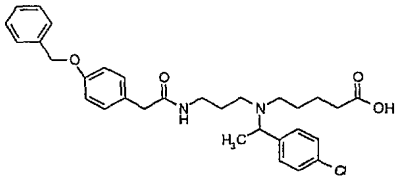
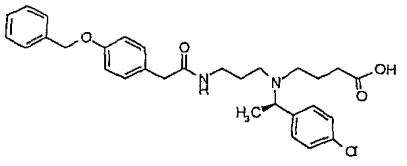
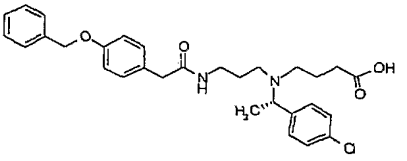
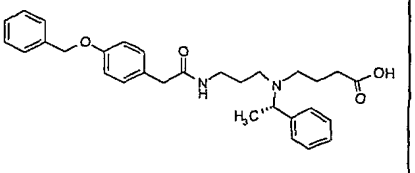
75		ES^+	471	$[M+H]^+$
76		ES^+	486	$[M+H]^+$
77		ES^+	453	$[M+H]^+$
78		ES^+	452	$[M+H]^+$
79		ES^+	496	$[M+H]^+$
80		ES^+	486	$[M+H]^+$

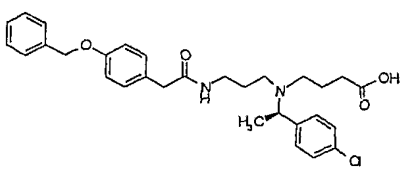
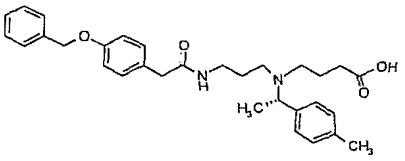
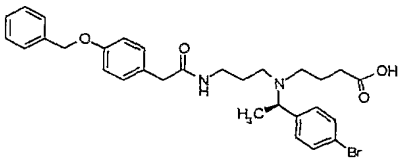
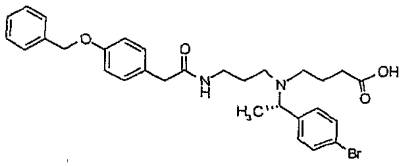
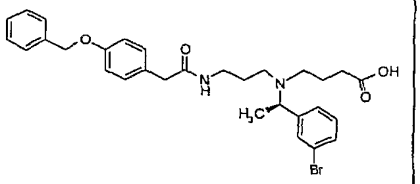
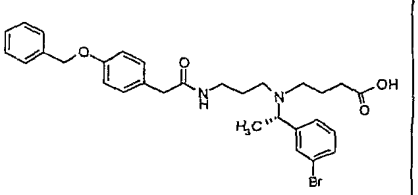
81		ES^+	531	$[M+H]^+$
82		ES^+	553	$[M+H]^+$
83		ES^+	554	$[M+H]^+$
84		ES^+	485	$[M+H]^+$
85		ES^+	460	$[M+H]^+$
86		ES^+	510	$[M+H]^+$

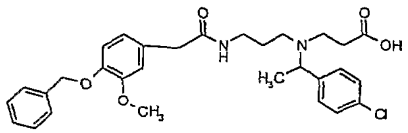
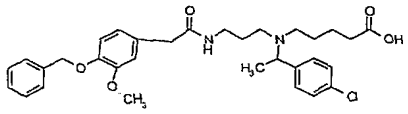
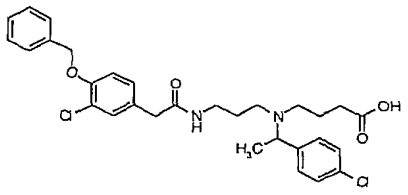
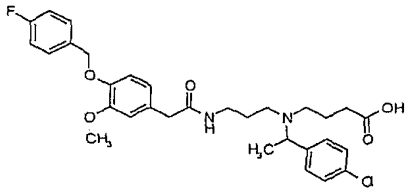
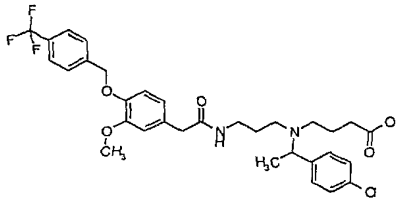
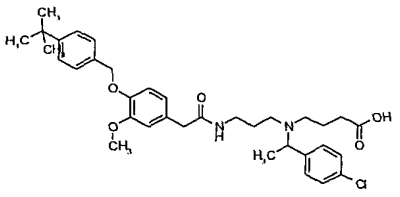
87		ES^+	553	$[M+H]^+$
88		ES^+	468	$[M+H]^+$
89		ES^+	468	$[M+H]^+$
90		ES^+	493	$[M+H]^+$
91		ES^+	536	$[M+H]^+$
92		ES^+	536	$[M+H]^+$

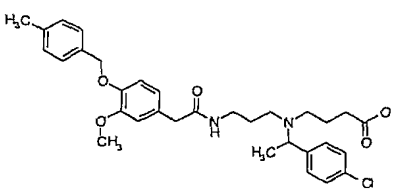
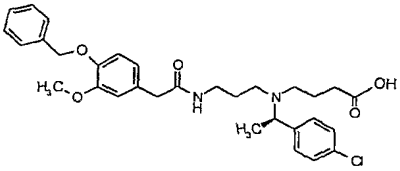
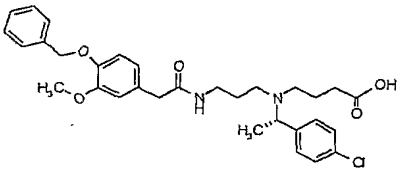
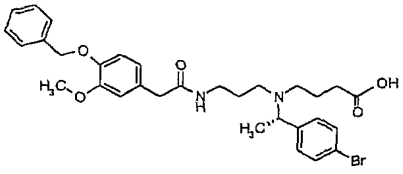
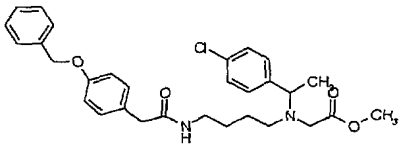
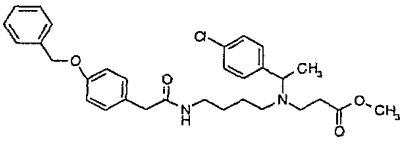
93		ES^+	461	$[M+H]^+$
94		ES^-	445	$[M-H]^-$
95		ES^+	461	$[M+H]^+$
96		ES^+	490	$[M+H]^+$
97		ES^+	524	$[M+H]^+$
98		ES^-	543	$[M+H]^+$

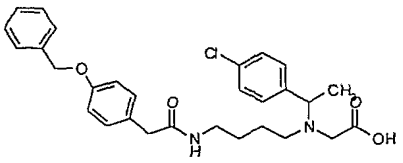
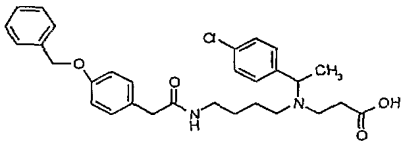
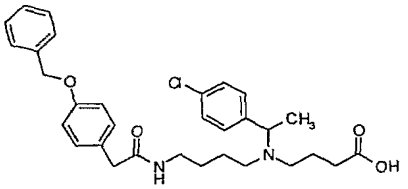
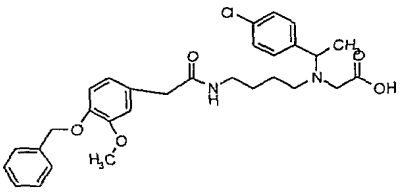
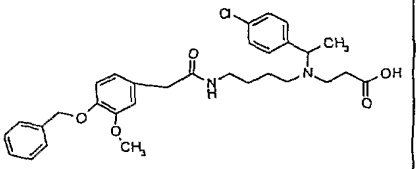
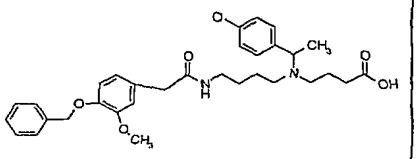
99		ES^+	553	$[M+H]^+$
100		ES^+	471	$[M+H]^+$
101		ES^+	501	$[M+H]^+$
102		ES^-	501	$[M+H]^-$
103		ES^+	464	$[M+H]^+$
104		ES^+	524	$[M+H]^+$

105		ES^+	552	$[M+H]^+$
106		ES^+	510	$[M+H]^+$
107		ES^+	538	$[M+H]^+$
108		ES^+	524	$[M+H]^+$
109		ES^+	524	$[M+H]^+$
110		ES^+	489	$[M+H]^+$

111		ES^+	503	$[M+H]^+$
112		ES^+	503	$[M+H]^+$
113		ES^+	569	$[M+H]^+$
114		ES^-	569	$[M+H]^+$
115		ES^+	569	$[M+H]^+$
116		ES^+	569	$[M+H]^+$

117		ES^-	540	$[M+H]^+$
118		ES^+	568	$[M+H]^+$
119		ES^+	558	$[M+H]^+$
120		ES^+	572	$[M+H]^+$
121		ES^-	622	$[M+H]^+$
122		ES^+	610	$[M+H]^+$

123		ES^+	568	$[M+H]^+$
124		ES^-	554	$[M+H]^+$
125		ES^+	554	$[M+H]^+$
126		ES^+	599	$[M+H]^+$
127		ES^+	524	$[M+H]^-$
128		ES^+	538	$[M+H]^+$

129		ES^+	510	$[M+H]^+$
130		ES^+	524	$[M+H]^+$
131		ES^+	538	$[M+H]^+$
132		ES^-	540	$[M+H]^+$
133		ES^+	554	$[M+H]^+$
134		ES^+	568	$[M+H]^+$

Example 8. Chemotaxis Assay

The inhibitory activity of the compounds against eotaxin-induced chemotaxis was determined by chemotaxis assay using eotaxin and human CCR-3 transfectant cells (CCR3/U937), as described by Ohashi, H. *et al.*, *Int Arch Allergy Immunol.* (1999) 118, 44-50 with minor modification. CCR-3 transfectant cells were grown in RPMI1640 medium containing 10% fetal calf serum (FCS) and Genetecin 418 (0.8 mg/ml). For the assay, CCR-3 transfectant cells were isolated and resuspended at 1 x 10^7 cells/ml in assay medium (RPMI 1640 medium containing 0.1 % bovine serum albumin (BSA)). The chemotaxis assay was performed in a 24-well culture plate. Human eotaxin suspended in assay medium was added to the wells at 1 x 10^{-9} M along with test compounds at various concentrations. For a positive control, eotaxin was added to the wells without a test compound, and for a negative control, neither eotaxin nor a test compound was added to the wells. Chemotaxicell (Kurabo Co., Ltd.) having 5 micrometers pore size were inserted into each well and 100 micro liters of CCR-3 transfectant cells suspension were added to the top chamber. The plates were incubated at 37 °C for 1 hour. After incubation, migrated cells in lower wells were diluted and counted by particle size distribution analyzer (CDP-500, Sysmex Co., Ltd.).

The results shown in Table 2 indicate that the disclosed compounds inhibit eotaxin-induced chemotaxis.

Table 2

Compound No.	Inhibitory activity (%inhibition at 10μM)
1	95
2	52
3	63
4	70
5	40

Compound No.	Inhibitory activity (%inhibition at 10μM)
6	100
7	100
8	100
9	99
10	97
11	96
12	100
13	88
14	97
15	97
16	94
17	94
18	95
19	98
20	95
21	95
22	92
23	93
24	94
25	88
26	98
27	84
28	86
29	96
30	50
31	97
32	33
33	25

Compound No.	Inhibitory activity (%inhibition at 10μM)
34	45
35	100
36	86
37	100
38	96
39	70
40	100
41	100
42	100
43	100
44	100
45	100
46	100
47	100
48	61
49	90
50	83
51	100
52	99
53	100
54	98
55	100
56	63
57	44
58	46
59	19
60	84
61	88

Compound No.	Inhibitory activity (%inhibition at 10μM)
62	97
63	100
64	40
65	69
66	85
67	83
68	93
69	71
70	36
71	67
72	99
73	87
74	44
75	64
76	72
77	75
78	46
79	85
80	95
81	22
82	97
83	78
84	73
85	96
86	100
87	100
88	100
89	100

Compound No.	Inhibitory activity (%inhibition at 10μM)
90	96
91	96
92	100
93	94
94	75
95	100
96	100
97	51
98	75
99	100
100	96
101	92
102	100
103	100
104	98
105	100
106	99
107	100
108	56
109	100
110	82
111	31
112	100
113	74
114	100
115	20
116	100
117	100

Compound No.	Inhibitory activity (%inhibition at 10μM)
118	100
119	100
120	100
121	98
122	96
123	100
124	42
125	100
126	100
127	67
128	55
129	94
130	90
131	91
132	95
133	71
134	82

Example 9. Suppression of Eosinophil Infiltration in Bronchoalveolar Lavage Fluid (BALF) by Compound No. 12

Male BALB/c mice were immunized by an intraperitoneal injection of 10 μg OVA adsorbed to 1 mg aluminum hydroxide gel (alum). A booster injection of the same dose of alum-adsorbed OVA was given 5 days later. Unimmunized control mice received saline.

Twelve days after primary immunization, both the immunized and unimmunized mice were exposed to aerosolized antigen. Aerosolization of OVA

was performed using a nose-only aerosol chamber adapted for mice. Animals were exposed for 10 minutes to 5 mg/ml OVA aerosolized by an ultrasonic nebulizer (NE-U12, Omron, Tokyo, Japan) driven by a vacuum pump. The antigen bronchoprovocation was repeated on day 16 and day 20 under the same conditions. Compound No. 12 (CPD No. 12) was dissolved in saline containing 2 % DMSO and 2 % Cremophore and administered intraperitoneally for 9 days, starting on the first day of antigen inhalation.

Twenty-four hours after the final aerosol exposure, bronchoalveolar lavage fluid (BALF) was collected by lavaging whole-lung three times with 0.7-ml aliquots of physiological saline containing 0.1% BSA via the tracheal cannula while gently massaging the thorax. The BALF recovered from one mouse was pooled, centrifuged, and the cells were resuspended in 100 μl saline containing 0.1% BSA. Cell numbers were determined using a hemocytometer and 2 x 10^4 cells were cytecetrifuged onto a glass slide. Cells were stained with Diff-Quik (International reagent, Kobe, Japan), and cell types were identified by morphological criteria. Two hundred cells were examined per slide for differential count. As shown in Figure 1, Compound No. 12 (CPD No. 12) significantly suppressed eosinophil infiltration to bronchoalveolar lavage fluid (BALF).

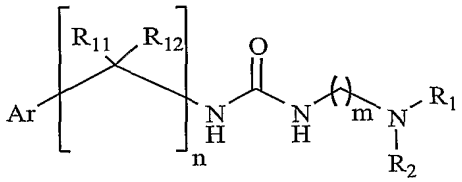
Example 10. Suppression of Eosinophil Infiltration to Bronchoalveolar Lavage Fluid (BALF) by Compound 87

Male BALB/c mice were immunized by an intraperitoneal injection of 10 μg OVA adsorbed to 1 mg aluminium hydroxide gel (alum). A booster injection of the same dose of alum-adsorbed OVA was given 5 days later. Twelve days after primary immunization, eotaxin was given to the immunized mice intratracheally. Compound 87 was dissolved in water containing 0.5% $NaHCO_3$ and administered per oral 30 minutes before eotaxin administration.

Twenty-four hours after eotaxin administration, bronchoalveolar lavage fluid (BALF) was collected by lavaging whole-lung three times with 0.7-ml aliquots of physiological saline containing 0.1% BSA via the tracheal cannula while gently massaging the thorax. The BALF recovered from one mouse was pooled, centrifuged, and the cells were resuspended in 100 μl saline containing 0.1%BSA. Cell numbers were determined using a hemocytometer and 2 x 10^4 cells were cytecentrifuged onto a glass slide. Cells were stained with Diff-Qick (International Reagent, Kobe, Japan), and cell types were identified by morphological criteria. Two hundred cells were examined per slide for differential count. As shown in Figure 2., Compound 87 significantly suppressed eosinophil infiltration to BALF.

WE CLAIM

1. A compound of the Formula (I)



(I)

or a salt, hydrate, or stereoisomer thereof, wherein:

n is 0 or 1;

m is 2, 3, 4, or 5;

R11 and R12 are independently selected from the group consisting of hydrogen, halogen, alkyl, aryl and heteroaryl

wherein the alkyl, aryl or heteroaryl is optionally substituted with one or more groups independently selected from the group of consisting of hydrogen, hydroxy, halogen, trihalomethyl, alkyl, alkoxy, cyano, nitro, amino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, and cyanoguanidino;

Ar is aryl or heteroaryl

optionally substituted with one or more groups independently selected from the group consisting of hydroxy, halogen, trihalomethyl,

optionally substituted with one or more groups independently selected from the group consisting of hydroxy, halogen, trihalomethyl, trihalomethoxy, alkyl, alkoxy, cyano, nitro, amino, carboxy, alkyloxycarbonyl, arylmethyloxycarbonyl, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, cyanoguanidino, aryl

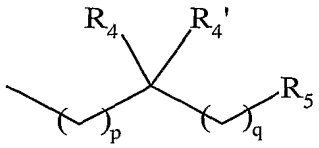
optionally substituted with one or more groups independently selected from the group consisting of hydroxy, halogen, trihalomethyl, alkyl, alkoxy, cyano, nitro, amino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, and cyanoguanidino, aryloxy

optionally substituted with one or more groups independently selected from the group consisting of hydroxy, halogen, trihalomethyl, alkyl, alkoxy, cyano, nitro, amino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, and cyanoguanidino, and heteroaryl

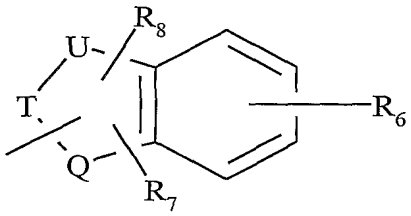
optionally substituted with one or more groups independently selected from the group consisting of hydroxy, halogen, trihalomethyl, alkyl, alkoxy, cyano, nitro, amino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl,

alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, and cyanoguanidino;

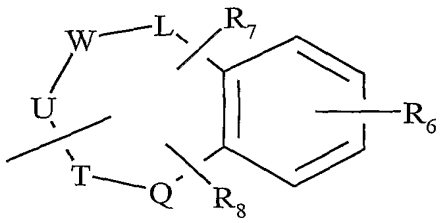
R_1 is:



or



or



p is 0, 1 or 2;

q is 0, 1 or 2;

R_4 and R_4' are independently selected from the group consisting of hydrogen, halogen, alkyl, aryl, heteroaryl

wherein the aryl or heteroaryl is optionally substituted with one or more groups independently selected from the group of consisting of hydrogen, hydroxy, halogen, trihalomethyl, alkyl, alkoxy, cyano, nitro, amino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, and cyanoguanidino;

and COR_9; wherein R_9 is hydroxy, alkyl, alkoxy, amino, alkylamino or arylamino;

R_5 is aryl or heteroaryl

optionally substituted with one or more groups independently selected from the group consisting of hydroxy, halogen, trihalomethyl, alkyl, alkoxy, cyano, nitro, amino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, cyanoguanidino, aryl

optionally substituted with one or more groups independently selected from the group consisting of hydroxy, halogen, trihalomethyl, alkyl, alkoxy, cyano, nitro, amino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, and cyanoguanidino,

and aryloxy

optionally substituted with one or more groups independently selected from the group consisting of hydroxy, halogen, trihalomethyl, alkyl, alkoxy, cyano, nitro, amino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl,

alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, and cyanoguanidino;

R_6 is selected from the group consisting of hydrogen, hydroxy, halogen, trihalomethyl, alkyl, alkoxy, cyano, nitro, amino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, cyanoguanidino, aryl

optionally substituted with one or more groups independently selected from the group consisting of hydroxy, halogen, trihalomethyl, alkyl, alkoxy, cyano, nitro, amino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, and cyanoguanidino,

and aryloxy

optionally substituted with one or more groups independently selected from the group consisting of hydroxy, halogen, trihalomethyl, alkyl, alkoxy, cyano, nitro, amino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, and cyanoguanidino;

R_7 and R_8 are independently selected from the group consisting of hydrogen, hydroxy, halogen, trihalomethyl, alkyl, alkoxy, cyano, nitro, amino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide,

arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, and cyanoguanidino;

Q, T, U, W and L are independently selected from the group of atoms consisting of C, N, O and S; wherein adjacent atoms U-T, T-Q, U-W, W-L may form one or more double bonds, and wherein no pair of said adjacent atoms forms O-O or S-S;

R_2 is selected from the group consisting of alkyl, alkenyl and alkynyl

optionally substituted with one or more groups independently selected from the group consisting of carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, alkylsulfonylcarbamoyl, arylsulfonylcarbamoyl, alkyloxycarbonyl, tetrazolyl, isoxazolyl, isothiazolyl, alkylsulfonamido, arylsulfonamido, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylsulfonamide, arylsulfonamide, alkylthio, halogen, acyloxy, hydroxy, nitro, amino, acylamino, alkylamino, cyano,

aryl

optionally substituted with one or more groups independently selected from the group consisting of alkyl or alkoxy, wherein the alkyl or alkoxy may be optionally substituted with carboxy or alkyloxycarbonyl, cyano, nitro, amino, acylamino, alkylamino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, alkylsulfonylcarbamoyl, arylsulfonylcarbamoyl, alkyloxycarbonyl, tetrazolyl, isoxazolyl, isothiazolyl, alkylsulfonamido, arylsulfonamido, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylsulfonamide, arylsulfonamide, alkylthio, acyl, acyloxy, aryloxy, arylmethyloxy, hydrazino, hydroxyamino, amidino, guanidino, cyanoguanidino, hydroxy, and halogen,

heteroaryl

optionally substituted with one or more groups independently selected from the group consisting of alkyl or alkoxy which may be optionally substituted with carboxy or alkyloxycarbonyl, cyano, nitro, amino, acylamino, alkylamino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, alkylsulfonylcarbamoyl, arylsulfonylcarbamoyl, alkyloxycarbonyl, tetrazolyl, isoxazolyl, isothiazolyl, alkylsulfonamido, arylsulfonamido, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylsulfonamide, arylsulfonamide, alkylthio, acyl, acyloxy, hydrazino, hydroxyamino, amidino, guanidino, cyanoguanidino, hydroxy, and halogen,

alkoxy

optionally substituted with one or more groups independently selected from the group consisting of alkyl or alkoxy which may be optionally substituted with carboxy or alkyloxycarbonyl, cyano, nitro, amino, acylamino, alkylamino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, alkylsulfonylcarbamoyl, arylsulfonylcarbamoyl, alkyloxycarbonyl, tetrazolyl, isoxazolyl, isothiazolyl, alkylsulfonamido, arylsulfonamido, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylsulfonamide, arylsulfonamide, alkylthio, acyl, acyloxy, hydrazino, hydroxyamino, amidino, guanidino, cyanoguanidino, hydroxy, and halogen,

arylmethyloxy

optionally substituted with one or more groups independently selected from the group consisting of alkyl or alkoxy which is optionally substituted with carboxy or alkyloxycarbonyl, cyano, nitro, amino, acylamino, alkylamino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, alkylsulfonylcarbamoyl, arylsulfonylcarbamoyl,

alkyloxycarbonyl, tetrazolyl, isoxazolyl, isothiazolyl, alkylsulfonamido, arylsulfonamido, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylsulfonamide, arylsulfonamide, alkylthio, acyl, acyloxy, hydrazino, hydroxyamino, amidino, guanidino, cyanoguanidino, hydroxy, and halogen,

cycloalkyl

optionally substituted with one or more groups independently selected from the group consisting of alkyl or alkoxy which is optionally substituted with carboxy or alkyloxycarbonyl, cyano, nitro, amino, acylamino, alkylamino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, alkylsulfonylcarbamoyl, arylsulfonylcarbamoyl, alkyloxycarbonyl, tetrazolyl, isoxazolyl, isothiazolyl, alkylsulfonamido, arylsulfonamido, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylsulfonamide, arylsulfonamide, alkylthio, acyl, acyloxy, hydrazino, hydroxyamino, amidino, guanidino, cyanoguanidino, hydroxy, and halogen,

and heterocycle;

provided that no bond is formed between R_1 and R_2.

2. The compound according to claim 1, wherein m is 3, 4, or 5.

3. The compound according to claim 2, wherein m is 3 or 4.

4. The compound according to claim 3, wherein Ar is aryl optionally substituted with one or more groups independently selected from the group consisting of hydroxy, halogen, trihalomethyl, trihalomethoxy, alkyl, alkoxy, cyano, nitro, amino, carboxy, alkyloxycarbonyl, arylmethyloxycarbonyl,

carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, cyanoguanidino, aryl

optionally substituted with one or more groups independently selected from the group consisting of hydroxy, halogen, trihalomethyl, alkyl, alkoxy, cyano, nitro, amino, and carboxy,

and aryloxy

optionally substituted with one or more groups independently selected from the group consisting of hydroxy, halogen, trihalomethyl, alkyl, alkoxy, cyano, nitro, amino, and carboxy;

R_5 is aryl or heteroaryl

optionally substituted with one or more groups independently selected from the group consisting of hydroxy, halogen, trihalomethyl, alkyl, alkoxy, cyano, nitro, amino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, cyanoguanidino, aryl

optionally substituted with one or more groups independently selected from the group consisting of hydroxy, halogen, trihalomethyl, alkyl, alkoxy, cyano, nitro, amino, and carboxy,

and aryloxy

optionally substituted with one or more groups independently selected from the group consisting of hydroxy, halogen, trihalomethyl, alkyl, alkoxy, cyano, nitro, amino, and carboxy;

R_6 is selected from the group consisting of hydrogen, hydroxy, halogen, trihalomethyl, alkyl, alkoxy, cyano, nitro, amino, and carboxy;

R_7 and R_8 are independently selected from the group consisting of hydrogen, hydroxy, halogen, trihalomethyl, alkyl, alkoxy, cyano, nitro, amino, and carboxy.

5. The compound of claim 4, wherein R_2 is independently selected from the group consisting of alkyl, alkenyl and alkynyl,

substituted with one or more groups independently selected from the group consisting of carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, alkylsulfonylcarbamoyl, arylsulfonylcarbamoyl, alkyloxycarbonyl, tetrazolyl, isoxazolyl, isothiazolyl, alkylsulfonamido, arylsulfonamido, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylsulfonamide, arylsulfonamide, acyloxy, acylamino, aryl

substituted with one or more groups independently selected from the group consisting of alkyl or alkoxy which are substituted with carboxy or alkyloxycarbonyl, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, alkylsulfonylcarbamoyl, arylsulfonylcarbamoyl, alkyloxycarbonyl, tetrazolyl, isoxazolyl, isothiazolyl, alkylsulfonamido, arylsulfonamido, sulfonyl, alklylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylsulfonamide, arylsulfonamide, aryloxy, arylmethyloxy, acylamino, hydroxy, and halogen,

heteroaryl

substituted with one or more groups independently selected from the group consisting of alkyl or alkoxy which are substituted with carboxy or alkyloxycarbonyl, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, alkylsulfonylcarbamoyl, arylsulfonylcarbamoyl, alkyloxycarbonyl, tetrazolyl, isoxazolyl, isothiazolyl, alkylsulfonamido, arylsulfonamido, sulfonyl, alklylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylsulfonamide, arylsulfonamide, acylamino, hydroxy, and halogen,

alkoxy

optionally substituted with one or more groups independently selected from the group consisting of alkyl or alkoxy which may be optionally substituted with carboxy or alkyloxycarbonyl, cyano, nitro, amino, acylamino, alkylamino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, alkylsulfonylcarbamoyl, arylsulfonylcarbamoyl, alkyloxycarbonyl, tetrazolyl, isoxazolyl, isothiazolyl, alkylsulfonamido, arylsulfonamido, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylsulfonamide, arylsulfonamide, alkylthio, acyl, acyloxy, hydrazino, hydroxyamino, amidino, guanidino, cyanoguanidino, hydroxy, and halogen,

arylmethyloxy

substituted with one or more groups independently selected from the group consisting of alkyl or alkoxy which are substituted with carboxy or alkyloxycarbonyl, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, alkylsulfonylcarbamoyl, arylsulfonylcarbamoyl, alkyloxycarbonyl, tetrazolyl, isoxazolyl, isothiazolyl, alkylsulfonamido, arylsulfonamido, sulfonyl, alklylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylsulfonamide, arylsulfonamide, acylamino, hydroxy, and halogen,

and cycloalkyl

substituted with one or more groups independently selected from the group consisting of alkyl or alkoxy which is substituted with carboxy or alkyloxycarbonyl, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, alkylsulfonylcarbamoyl, arylsulfonylcarbamoyl, alkyloxycarbonyl, tetrazolyl, isoxazolyl, isothiazolyl, alkylsulfonamido, arylsulfonamido, sulfonyl, alklylsulfonyl,

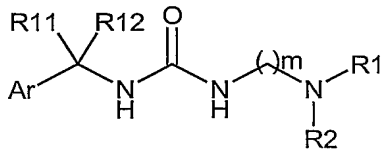
arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylsulfonamide, arylsulfonamide, and acylamino.

6. The compound of claim 5, wherein R_2 is independently selected from the group consisting of alkyl, alkenyl and alkynyl,

substituted with one or more groups independently selected from the group consisting of carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, alkylsulfonylcarbamoyl, arylsulfonylcarbamoyl, alkyloxycarbonyl, tetrazolyl, isoxazolyl, isothiazolyl, alkylsulfonamido, arylsulfonamido, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylsulfonamide, arylsulfonamide, and acylamino.

7. The compound of claim 6, wherein R_2 is independently selected from the group consisting of alkyl, alkenyl and alkynyl, substituted with one or more groups independently selected from the group consisting of carboxy and alkyloxycarbonyl.

8. A compound of the Formula (II)



(II)

or a salt, hydrate, or stereoisomer thereof, wherein:

m is 2, 3, 4 or 5;

R11 and R12 are independently selected from the group consisting of hydrogen, halogen, C_{1-5} alkyl, aryl and heteroaryl

wherein the alkyl, aryl or heteroaryl is optionally substituted with one or more groups independently selected from the group of consisting of hydrogen, hydroxy, halogen, trihalomethyl, alkyl, alkoxy, cyano, nitro, amino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, and cyanoguanidino;

Ar is aryl or heteroaryl

optionally substituted with one or more groups independently selected from the group consisting of hydroxy, halogen, trihalomethyl, trihalomethoxy, alkyl, alkoxy, cyano, nitro, amino, carboxy, alkyloxycarbonyl, arylmethyloxycarbonyl, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, cyanoguanidino, aryl

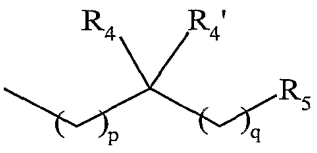
optionally substituted with one or more groups independently selected from the group consisting of hydroxy, halogen, trihalomethyl, alkyl, alkoxy, cyano, nitro, amino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, and cyanoguanidino, aryloxy

optionally substituted with one or more groups independently selected from the group consisting of hydroxy, halogen, trihalomethyl, alkyl, alkoxy, cyano, nitro, amino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl,

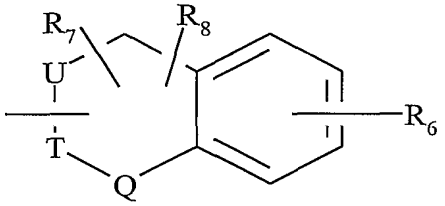
alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, and cyanoguanidino, and heteroaryl

optionally substituted with one or more groups independently selected from the group consisting of hydroxy, halogen, trihalomethyl, alkyl, alkoxy, cyano, nitro, amino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, and cyanoguanidino;

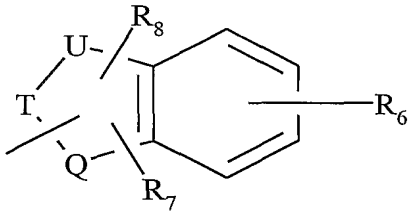
R_1 is:



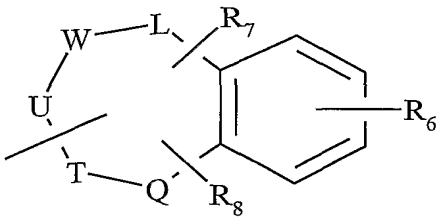
or



or



or



p is 0, 1 or 2;

q is 0, 1 or 2;

R_4 and R_4' are independently selected from the group consisting of hydrogen, halogen, alkyl, aryl, heteroaryl

wherein the aryl or heteroaryl is optionally substituted with one or more groups independently selected from the group of consisting of hydrogen, hydroxy, halogen, trihalomethyl, alkyl, alkoxy, cyano, nitro, amino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy,

sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, and cyanoguanidino;

and COR_9; wherein R_9 is hydroxy, alkyl, alkoxy, amino, alkylamino or arylamino;

R_5 is aryl or heteroaryl

optionally substituted with one or more groups independently selected from the group consisting of hydroxy, halogen, trihalomethyl, alkyl, alkoxy, cyano, nitro, amino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, cyanoguanidino, aryl

optionally substituted with one or more groups independently selected from the group consisting of hydroxy, halogen, trihalomethyl, alkyl, alkoxy, cyano, nitro, amino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, and cyanoguanidino, and aryloxy

optionally substituted with one or more groups independently selected from the group consisting of hydroxy, halogen, trihalomethyl, alkyl, alkoxy, cyano, nitro, amino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, and cyanoguanidino;

R_6 is selected from the group consisting of hydrogen, hydroxy, halogen, trihalomethyl, alkyl, alkoxy, cyano, nitro, amino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, cyanoguanidino, aryl

optionally substituted with one or more groups independently selected from the group consisting of hydroxy, halogen, trihalomethyl, alkyl, alkoxy, cyano, nitro, amino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, and cyanoguanidino,

and aryloxy

optionally substituted with one or more groups independently selected from the group consisting of hydroxy, halogen, trihalomethyl, alkyl, alkoxy, cyano, nitro, amino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, and cyanoguanidino;

R_7 and R_8 are independently selected from the group consisting of hydrogen, hydroxy, halogen, trihalomethyl, alkyl, alkoxy, cyano, nitro, amino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, and cyanoguanidino;

Q, T, U, W and L are independently selected from the group of atoms consisting of C, N, O and S; wherein adjacent atoms U-T, T-Q, U-W, W-L may

form one or more double bonds, and wherein no pair of said adjacent atoms forms O-O or S-S;

R_2 is selected from the group consisting of alkyl, alkenyl and alkynyl

optionally substituted with one or more groups independently selected from the group consisting of carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, alkylsulfonylcarbamoyl, arylsulfonylcarbamoyl, alkyloxycarbonyl, tetrazolyl, isoxazolyl, isothiazolyl, alkylsulfonamido, arylsulfonamido, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylsulfonamide, arylsulfonamide, alkylthio, halogen, acyloxy, hydroxy, nitro, amino, acylamino, alkylamino, cyano, aryl

optionally substituted with one or more groups independently selected from the group consisting of alkyl or alkoxy, wherein the alkyl or alkoxy may be optionally substituted with carboxy or alkyloxycarbonyl, cyano, nitro, amino, acylamino, alkylamino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, alkylsulfonylcarbamoyl, arylsulfonylcarbamoyl, alkyloxycarbonyl, tetrazolyl, isoxazolyl, isothiazolyl, alkylsulfonamido, arylsulfonamido, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylsulfonamide, arylsulfonamide, alkylthio, acyl, acyloxy, aryloxy, arylmethyloxy, hydrazino, hydroxyamino, amidino, guanidino, cyanoguanidino, hydroxy, and halogen,

heteroaryl

optionally substituted with one or more groups independently selected from the group consisting of alkyl or alkoxy which may be optionally substituted with carboxy or alkyloxycarbonyl, cyano, nitro, amino, acylamino, alkylamino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, alkylsulfonylcarbamoyl, arylsulfonylcarbamoyl,

alkyloxycarbonyl, tetrazolyl, isoxazolyl, isothiazolyl, alkylsulfonamido, arylsulfonamido, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylsulfonamide, arylsulfonamide, alkylthio, acyl, acyloxy, hydrazino, hydroxyamino, amidino, guanidino, cyanoguanidino, hydroxy, and halogen,

alkoxy

optionally substituted with one or more groups independently selected from the group consisting of alkyl or alkoxy which may be optionally substituted with carboxy or alkyloxycarbonyl, cyano, nitro, amino, acylamino, alkylamino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, alkylsulfonylcarbamoyl, arylsulfonylcarbamoyl, alkyloxycarbonyl, tetrazolyl, isoxazolyl, isothiazolyl, alkylsulfonamido, arylsulfonamido, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylsulfonamide, arylsulfonamide, alkylthio, acyl, acyloxy, hydrazino, hydroxyamino, amidino, guanidino, cyanoguanidino, hydroxy, and halogen,

arylmethyloxy

optionally substituted with one or more groups independently selected from the group consisting of alkyl or alkoxy which is optionally substituted with carboxy or alkyloxycarbonyl, cyano, nitro, amino, acylamino, alkylamino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, alkylsulfonylcarbamoyl, arylsulfonylcarbamoyl, alkyloxycarbonyl, tetrazolyl, isoxazolyl, isothiazolyl, alkylsulfonamido, arylsulfonamido, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylsulfonamide, arylsulfonamide, alkylthio, acyl, acyloxy,

hydrazino, hydroxyamino, amidino, guanidino, cyanoguanidino, hydroxy, and halogen,

cycloalkyl

optionally substituted with one or more groups independently selected from the group consisting of alkyl or alkoxy which is optionally substituted with carboxy or alkyloxycarbonyl, cyano, nitro, amino, acylamino, alkylamino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, alkylsulfonylcarbamoyl, arylsulfonylcarbamoyl, alkyloxycarbonyl, tetrazolyl, isoxazolyl, isothiazolyl, alkylsulfonamido, arylsulfonamido, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylsulfonamide, arylsulfonamide, alkylthio, acyl, acyloxy, hydrazino, hydroxyamino, amidino, guanidino, cyanoguanidino, hydroxy, and halogen,

and heterocycle;

provided that no bond is formed between R_1 and R_2.

9. The compound according to claim 8, wherein m is 3, 4, or 5.

10. The compound according to claim 9, wherein m is 3 or 4.

11. The compound according to claim 10, wherein Ar is aryl optionally substituted with one or more groups independently selected from the group consisting of hydroxy, halogen, trihalomethyl, trihalomethoxy, alkyl, alkoxy, cyano, nitro, amino, carboxy, alkyloxycarbonyl, arylmethyloxycarbonyl, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, cyanoguanidino, aryl

optionally substituted with one or more groups independently selected from the group consisting of hydroxy, halogen, trihalomethyl, alkyl, alkoxy, cyano, nitro, amino, and carboxy,

and aryloxy

optionally substituted with one or more groups independently selected from the group consisting of hydroxy, halogen, trihalomethyl, alkyl, alkoxy, cyano, nitro, amino, and carboxy;

R_5 is aryl or heteroaryl

optionally substituted with one or more groups independently selected from the group consisting of hydroxy, halogen, trihalomethyl, alkyl, alkoxy, cyano, nitro, amino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, cyanoguanidino, aryl

optionally substituted with one or more groups independently selected from the group consisting of hydroxy, halogen, trihalomethyl, alkyl, alkoxy, cyano, nitro, amino, and carboxy,

and aryloxy

optionally substituted with one or more groups independently selected from the group consisting of hydroxy, halogen, trihalomethyl, alkyl, alkoxy, cyano, nitro, amino, and carboxy;

R_6 is selected from the group consisting of hydrogen, hydroxy, halogen, trihalomethyl, alkyl, alkoxy, cyano, nitro, amino, and carboxy;

R_7 and R_8 are independently selected from the group consisting of hydrogen, hydroxy, halogen, trihalomethyl, alkyl, alkoxy, cyano, nitro, amino, and carboxy.

12. The compound of claim 11, wherein R_2 is independently selected from the group consisting of alkyl, alkenyl and alkynyl,

substituted with one or more groups independently selected from the group consisting of carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, alkylsulfonylcarbamoyl, arylsulfonylcarbamoyl, alkyloxycarbonyl, tetrazolyl, isoxazolyl, isothiazolyl, alkylsulfonamido, arylsulfonamido, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylsulfonamide, arylsulfonamide, acyloxy, acylamino, aryl

substituted with one or more groups independently selected from the group consisting of alkyl or alkoxy which are substituted with carboxy or alkyloxycarbonyl, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, alkylsulfonylcarbamoyl, arylsulfonylcarbamoyl, alkyloxycarbonyl, tetrazolyl, isoxazolyl, isothiazolyl, alkylsulfonamido, arylsulfonamido, sulfonyl, alklylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylsulfonamide, arylsulfonamide, aryloxy, arylmethyloxy, acylamino, hydroxy, and halogen,

heteroaryl

substituted with one or more groups independently selected from the group consisting of alkyl or alkoxy which are substituted with carboxy or alkyloxycarbonyl, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, alkylsulfonylcarbamoyl, arylsulfonylcarbamoyl, alkyloxycarbonyl, tetrazolyl, isoxazolyl, isothiazolyl, alkylsulfonamido, arylsulfonamido, sulfonyl, alklylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylsulfonamide, arylsulfonamide, acylamino, hydroxy, and halogen,

alkoxy

optionally substituted with one or more groups independently selected from the group consisting of alkyl or alkoxy which may be optionally substituted with carboxy or alkyloxycarbonyl, cyano, nitro, amino, acylamino, alkylamino, carboxy, carbamoyl, alkylcarbamoyl,

arylcarbamoyl, alkylsulfonylcarbamoyl, arylsulfonylcarbamoyl, alkyloxycarbonyl, tetrazolyl, isoxazolyl, isothiazolyl, alkylsulfonamido, arylsulfonamido, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylsulfonamide, arylsulfonamide, alkylthio, acyl, acyloxy, hydrazino, hydroxyamino, amidino, guanidino, cyanoguanidino, hydroxy, and halogen,

arylmethyloxy

substituted with one or more groups independently selected from the group consisting of alkyl or alkoxy which are substituted with carboxy or alkyloxycarbonyl, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, alkylsulfonylcarbamoyl, arylsulfonylcarbamoyl, alkyloxycarbonyl, tetrazolyl, isoxazolyl, isothiazolyl, alkylsulfonamido, arylsulfonamido, sulfonyl, alklylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylsulfonamide, arylsulfonamide, acylamino, hydroxy, and halogen,

and cycloalkyl

substituted with one or more groups independently selected from the group consisting of alkyl or alkoxy which is substituted with carboxy or alkyloxycarbonyl, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, alkylsulfonylcarbamoyl, arylsulfonylcarbamoyl, alkyloxycarbonyl, tetrazolyl, isoxazolyl, isothiazolyl, alkylsulfonamido, arylsulfonamido, sulfonyl, alklylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylsulfonamide, arylsulfonamide, and acylamino.

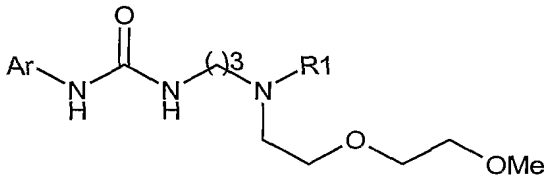
13. The compound of claim 12, wherein R_2 is independently selected from the group consisting of alkyl, alkenyl and alkynyl,

substituted with one or more groups independently selected from the group consisting of carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, alkylsulfonylcarbamoyl, arylsulfonylcarbamoyl, alkyloxycarbonyl, tetrazolyl, isoxazolyl, isothiazolyl, alkylsulfonamido, arylsulfonamido, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylsulfonamide, arylsulfonamide, and acylamino.

14. The compound of claim 13, wherein R_2 is independently selected from the group consisting of alkyl, alkenyl and alkynyl, substituted with one or more groups independently selected from the group consisting of carboxy and alkyloxycarbonyl.

15. The compound according to claim 8, wherein the compound is defined in Table 1A.

16. A compound of the Formula (III)



(III)

or a salt, hydrate, or stereoisomer thereof, wherein:

Ar is aryl or heteroaryl

optionally substituted with one or more groups independently selected from the group consisting of hydroxy, halogen, trihalomethyl, trihalomethoxy, alkyl, alkoxy, cyano, nitro, amino, carboxy, alkyloxycarbonyl, arylmethyloxycarbonyl, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl,

sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, cyanoguanidino, aryl

optionally substituted with one or more groups independently selected from the group consisting of hydroxy, halogen, trihalomethyl, alkyl, alkoxy, cyano, nitro, amino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, cyanoguanidino,

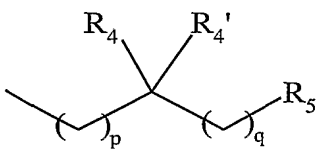
aryloxy

optionally substituted with one or more groups independently selected from the group consisting of hydroxy, halogen, trihalomethyl, alkyl, alkoxy, cyano, nitro, amino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, and cyanoguanidino,

and heteroaryl

optionally substituted with one or more groups independently selected from the group consisting of hydroxy, halogen, trihalomethyl, alkyl, alkoxy, cyano, nitro, amino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, and cyanoguanidino;

R_1 is:



p is 0, 1 or 2;

q is 0, 1 or 2;

R_4 and R_4' are independently selected from the group consisting of hydrogen, halogen, alkyl, aryl, heteroaryl

wherein the aryl or heteroaryl is optionally substituted with one or more groups independently selected from the group of consisting of hydrogen, hydroxy, halogen, trihalomethyl, alkyl, alkoxy, cyano, nitro, amino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, and cyanoguanidino;

and COR_9; wherein R_9 is hydroxy, alkyl, alkoxy, amino, alkylamino or arylamino;

R_5 is aryl or heteroaryl

optionally substituted with one or more groups independently selected from the group consisting of hydroxy, halogen, trihalomethyl, alkyl, alkoxy, cyano, nitro, amino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, cyanoguanidino, aryl

optionally substituted with one or more groups independently selected from the group consisting of hydroxy, halogen, trihalomethyl, alkyl, alkoxy, cyano, nitro, amino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, and cyanoguanidino,

and aryloxy

optionally substituted with one or more groups independently selected from the group consisting of hydroxy, halogen, trihalomethyl, alkyl, alkoxy, cyano, nitro, amino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, and cyanoguanidino.

17. The compound according to claim 16, wherein Ar is aryl optionally substituted with one or more groups independently selected from the group consisting of hydroxy, halogen, trihalomethyl, trihalomethoxy, alkyl, alkoxy, cyano, nitro, amino, carboxy, alkyloxycarbonyl, arylmethyloxycarbonyl, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, cyanoguanidino, aryl

optionally substituted with one or more groups independently selected from the group consisting of hydroxy, halogen, trihalomethyl, alkyl, alkoxy, cyano, nitro, amino, and carboxy,

and aryloxy

optionally substituted with one or more groups independently selected from the group consisting of hydroxy, halogen, trihalomethyl, alkyl, alkoxy, cyano, nitro, amino, and carboxy;

R_5 is aryl or heteroaryl

optionally substituted with one or more groups independently selected from the group consisting of hydroxy, halogen, trihalomethyl, alkyl, alkoxy, cyano, nitro, amino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl,

alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, cyanoguanidino, aryl

optionally substituted with one or more groups independently selected from the group consisting of hydroxy, halogen, trihalomethyl, alkyl, alkoxy, cyano, nitro, amino, and carboxy, and aryloxy

optionally substituted with one or more groups independently selected from the group consisting of hydroxy, halogen, trihalomethyl, alkyl, alkoxy, cyano, nitro, amino, and carboxy.

18. The compound according to claim 16, wherein the compound is defined in Table 1B:

19. A pharmaceutical composition comprising a compound according to claim 1.

20. A method of treating CCR-3 mediated diseases in a patient, comprising administering to said patient an effective amount of the pharmaceutical composition of claim 19.

21. The method of claim 20, wherein said CCR-3 mediated disease is an eosinophil mediated allergic disease.

22. The method of claim 21, wherein said eosinophil mediated allergic disease is selected from the group consisting of asthma, rhinitis, eczema, inflammatory bowl diseases and parasitic infections.

23. The method of claim 20, wherein said CCR-3 mediated disease is a T-cell or a dendritic cell mediated disease.

24. The method of claim 23, wherein said T-cell or dendritic cell mediated disease is selected from the group consisting of autoimmune diseases and HIV.

25. The method of claim 20, wherein said pharmaceutical composition comprises a prodrug.

26. A kit for treating CCR-3 mediated diseases in a patient, comprising:

(A) the pharmaceutical composition of claim 19;

(B) reagents to effect administration of said pharmaceutical composition to said patient; and

(C) instruments to effect administration of said pharmaceutical composition to said patient.

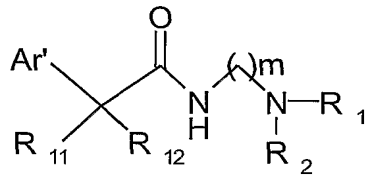
27. A method of inhibiting a CCR-3 mediated cellular response in a cell which expresses CCR-3, comprising contacting said cell with a compound according to claim 1, such that said cellular response is inhibited.

28. A method according to claim 27, wherein the CCR-3 mediated cellular response is an intracellular calcium mobilization.

29. A method according to claim 28, wherein the CCR-3 mediated cellular response is a chemotaxis.

30. A method of treating a CCR-3 mediated diseases in a mammal, comprising administering to said mammal an effective amount of the pharmaceutical composition according to claim 20.

31. A compound of Formula (I')



(I')

or a salt, hydrate, or stereoisomer thereof, wherein:

m is 2, 3, 4 or 5;

R_{11} and R_{12} are independently selected from the group consisting of hydrogen, halogen, C_{1-5} alkyl, aryl and heteroaryl

wherein the C_{1-5} alkyl, aryl or heteroaryl is optionally substituted with one or more groups independently selected from the group of consisting of hydrogen, hydroxy, halogen, trihalomethyl, C_{1-5}alkyl, C_{1-5}alkoxy, cyano, nitro, amino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, and cyanoguanidino;

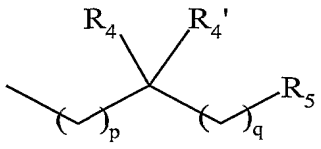
Ar' is aryl or heteroaryl

optionally substituted with one or more groups independently selected from the group consisting of hydroxy, halogen, trihalomethyl, trihalomethoxy, C_{1-5}alkyl, C_{1-5}alkoxy, cyano, nitro, amino, carboxy, alkyloxycarbonyl, arylmethyloxycarbonyl, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl,

sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, cyanoguanidino, aryl, aryloxy, heteroaryl, benzyloxy, benzoyl and naphthoyl

wherein the aryl, aryloxy, heteroaryl, benzyloxy, benzoyl or naphthoyl is optionally substituted with one or more groups independently selected from the group consisting of hydroxy, halogen, trihalomethyl, C_{1-5}alkyl, C_{1-5} alkoxy, cyano, nitro, amino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, and cyanoguanidino;

R_1 is:



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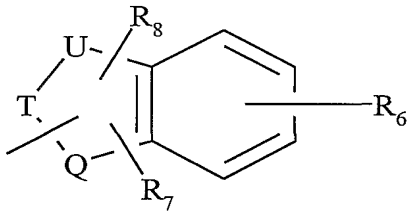

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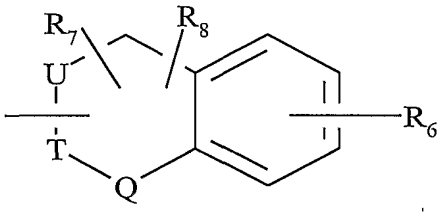
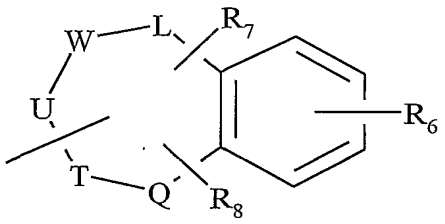


or



p is 0, 1 or 2;

q is 0, 1 or 2;

R_4 and R_4' are independently selected from the group consisting of hydrogen, halogen, C_{1-5} alkyl, aryl, heteroaryl

wherein the aryl or heteroaryl is optionally substituted with one or more groups independently selected from the group of consisting of hydrogen, hydroxy, halogen, trihalomethyl, C_{1-5} alkyl, C_{1-5}alkoxy, cyano, nitro, amino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, and cyanoguanidino

and COR_9, wherein R_9 is hydroxy, C_{1-5}alkyl, C_{1-5}alkoxy, amino, alkylamino or arylamino;

R_5 is aryl or heteroaryl

optionally substituted with one or more groups independently selected from the group consisting of hydroxy, halogen, trihalomethyl, C_{1-5} alkyl, C_{1-5} alkoxy, cyano, nitro, amino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, cyanoguanidino, aryl, and aryloxy

wherein the aryl or aryloxy is optionally substituted with one or more groups independently selected from the group consisting of hydroxy, halogen, trihalomethyl, C_{1-5} alkyl, C_{1-5} alkoxy, cyano, nitro, amino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, and cyanoguanidino;

R_6 is selected from the group consisting of hydrogen, hydroxy, halogen, trihalomethyl, C_{1-5} alkyl, C_{1-5} alkoxy, cyano, nitro, amino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, cyanoguanidino, aryl and aryloxy

wherein the aryl or aryloxy is optionally substituted with one or more groups independently selected from the group consisting of hydroxy, halogen, trihalomethyl, C_{1-5} alkyl, C_{1-5} alkoxy, cyano, nitro, amino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, cyanoguanidino;

R_7 and R_8 are independently selected from the group consisting of hydrogen, hydroxy, halogen, trihalomethyl, C_{1-5} alkyl, C_{1-5} alkoxy, cyano, nitro, amino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, and cyanoguanidino;

Q, T, U, W and L are independently selected from the group of atoms consisting of C, N, O and S; wherein adjacent atoms U-T, T-Q, U-W, W-L may form one or more double bonds, and wherein no pair of said adjacent atoms forms O-O or S-S;

R_2 is selected from the group consisting of C_{1-8} alkyl, C_{1-8} alkenyl and C_{1-8} alkynyl

optionally substituted with one or more groups independently selected from the group consisting of carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, alkylsulfonylcarbamoyl, arylsulfonylcarbamoyl, alkyloxycarbonyl, tetrazolyl, isoxazolyl, isothiazolyl, alkylsulfonamido, arylsulfonamido, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylsulfonamide, arylsulfonamide, alkylthio, halogen, acyloxy, hydroxy, nitro, amino, acylamino, alkylamino, cyano, aryl

optionally substituted with one or more groups independently selected from the group consisting of C_{1-5} alkyl or C_{1-5} alkoxy, wherein the alkyl or alkoxy may be optionally substituted with carboxy or alkyloxycarbonyl, cyano, nitro, amino, acylamino, alkylamino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, alkylsulfonylcarbamoyl, arylsulfonylcarbamoyl, alkyloxycarbonyl, tetrazolyl, isoxazolyl, isothiazolyl, alkylsulfonamido, arylsulfonamido, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylsulfonamide, arylsulfonamide,

alkylthio, acyl, acyloxy, aryloxy, arylmethyloxy, hydrazino, hydroxyamino, amidino, guanidino, cyanoguanidino, hydroxy, and halogen,

heteroaryl

optionally substituted with one or more groups independently selected from the group consisting of C_{1-5} alkyl or C_{1-5} alkoxy which may be optionally substituted with carboxy or alkyloxycarbonyl, cyano, nitro, amino, acylamino, alkylamino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, alkylsulfonylcarbamoyl, arylsulfonylcarbamoyl, alkyloxycarbonyl, tetrazolyl, isoxazolyl, isothiazolyl, alkylsulfonamido, arylsulfonamido, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylsulfonamide, arylsulfonamide, alkylthio, acyl, acyloxy, hydrazino, hydroxyamino, amidino, guanidino, cyanoguanidino, hydroxy, and halogen,

C_{1-5} alkoxy

optionally substituted with one or more groups independently selected from the group consisting of C_{1-5} alkyl or C_{1-5} alkoxy which may be optionally substituted with carboxy or alkyloxycarbonyl, cyano, nitro, amino, acylamino, alkylamino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, alkylsulfonylcarbamoyl, arylsulfonylcarbamoyl, alkyloxycarbonyl, tetrazolyl, isoxazolyl, isothiazolyl, alkylsulfonamido, arylsulfonamido, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylsulfonamide, arylsulfonamide, alkylthio, acyl, acyloxy, hydrazino, hydroxyamino, amidino, guanidino, cyanoguanidino, hydroxy, and halogen,

arylmethyloxy

optionally substituted with one or more groups independently selected from the group consisting of C_{1-5} alkyl or C_{1-5} alkoxy which is optionally substituted with carboxy or alkyloxycarbonyl, cyano, nitro, amino, acylamino, alkylamino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, alkylsulfonylcarbamoyl, arylsulfonylcarbamoyl, alkyloxycarbonyl, tetrazolyl, isoxazolyl, isothiazolyl, alkylsulfonamido, arylsulfonamido, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylsulfonamide, arylsulfonamide, alkylthio, acyl, acyloxy, hydrazino, hydroxyamino, amidino, guanidino, cyanoguanidino, hydroxy, and halogen,

C_{3-7} cycloalkyl

optionally substituted with one or more groups independently selected from the group consisting of C_{1-5} alkyl or C_{1-5} alkoxy which is optionally substituted with carboxy or alkyloxycarbonyl, cyano, nitro, amino, acylamino, alkylamino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, alkylsulfonylcarbamoyl, arylsulfonylcarbamoyl, alkyloxycarbonyl, tetrazolyl, isoxazolyl, isothiazolyl, alkylsulfonamido, arylsulfonamido, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylsulfonamide, arylsulfonamide, alkylthio, acyl, acyloxy, hydrazino, hydroxyamino, amidino, guanidino, cyanoguanidino, hydroxy, and halogen,

and heterocycle;

provided that no bond is formed between R_1 and R_2.

32. The compound according to claim 31, wherein:

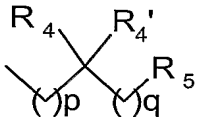
m is 3 or 4;

Ar' is aryl, optionally substituted with one or more groups independently selected from the group consisting of

hydroxy, halogen, trihalomethyl, C_{1-5}alkyl, C_{1-5}alkoxy, cyano, nitro, amino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, cyanoguanidino, aryl, aryloxy, benzyloxy, benzoyl, and naphthoyl, wherein the aryl, aryloxy, benzyloxy, benzoyl, or naphthoyl is optionally substituted with one or more groups independently selected from the group consisting of

hydroxy, halogen, trihalomethyl, C_{1-5}alkyl, C_{1-5}alkoxy, cyano, nitro, amino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino and cyanoguanidino;

R_1 is:



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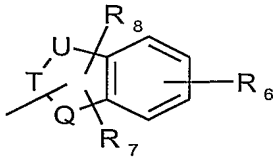
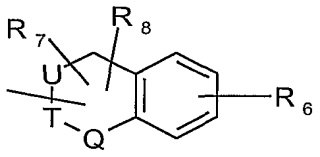




or

p is 0 or 1;

q is 0 or 1;

R_4 and R_4' is

hydrogen,

halogen,

or C_{1-3}alkyl;

R_5 is aryl, optionally substituted with one or more groups independently selected from the group consisting of

hydroxy, halogen, trihalomethyl, C_{1-5}alkyl, C_{1-5}alkoxy, cyano, nitro, amino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, and cyanoguanidino;

R_6 is hydrogen, hydroxy, halogen, trihalomethyl, C_{1-5}alkyl, C_{1-5}alkoxy, cyano, nitro, amino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino, or cyanoguanidino;

R_7 and R_8 is independently selected from the group consisting of hydrogen, hydroxy, halogen, trihalomethyl, C_{1-5}alkyl, C_{1-5}alkoxy, cyano, nitro, amino, carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, acyl, acyloxy, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylthio, alkylsulfonamide, arylsulfonamide, hydrazino, acylamino, alkylamino, hydroxyamino, amidino, guanidino and cyanoguanidino;

Q, T, U , W and L is independently selected from the group of atoms consisting of C, N, O and S. Two adjacent atoms of Q, T, U, W and L may make double bond(s), and no pair of such adjacent atoms forms O-O or S-S;

R_2 is selected from the group consisting of C_{1-8}alkyl, C_{1-8}alkenyl and C_{1-8}alkynyl, wherein the C_{1-8}alkyl, C_{1-8}alkenyl or C_{1-8}alkynyl is optionally substituted with one or more groups independently selected from the group consisting of carboxy, carbamoyl, alkylcarbamoyl, arylcarbamoyl, alkylsulfonylcarbamoyl, arylsulfonylcarbamoyl, alkyloxycarbonyl, tetrazolyl, isoxazolyl, isothiazolyl, alkylsulfonamido, arylsulfonamido, sulfonyl, alkylsulfonyl, arylsulfonyl, sulfamoyl, alkylsulfamoyl, arylsulfamoyl, alkylsulfonamide, arylsulfonamide, alkylthio, halogen, hydroxy, nitro, amino, acylamino, alkylamino, and cyano;

R_{11} and R_{12} are independently selected from the group consisting of hydrogen, halogen, and C_{1-3}alkyl.

33. The compound according to claim 32, wherein R_2 is selected from the group consisting of:

C_{1-5}alkyl, C_{1-5}alkenyl and C_{1-5}alkynyl, optionally substituted with one or more groups independently selected from the group consisting of carboxy, carbamoyl, alkylcarbamoyl, alkylsulfonylcarbamoyl, alkyloxycarbonyl, tetrazolyl, isoxazolyl, isothiazolyl, alkylsulfonamido,

arylsulfonamido, sulfonyl, alkylsulfonyl, sulfamoyl, alkylsulfamoyl, alkylsulfonamide, alkylthio, halogen, hydroxy, nitro, amino, acylamino, alkylamino, cyano,;

wherein R_4,R_5,R_6,R_7,R_8,R_{11}, R_{12}, U,T,Q,p,and q are defined as in claim 32.

34. The compound according to claim 33, wherein U, T and Q are carbon atoms; p and q are 0; and R_{11} and R_{12} are hydrogen or C_{1-3}alkyl.

35. The compound according to claim 34, wherein Ar' is aryl, optionally substituted with one or more groups independently selected from the group consisting of:

hydroxy, halogen, trihalomethyl, C_{1-5}alkyl, C_{1-5}alkoxy, cyano, nitro, amino, carboxy, benzyloxy, benzoyl, naphthoyl, aryl, wherein benzyloxy, benzoyl, or naphthoyl is optionally substituted with one or more groups independently selected from the group consisting of

hydroxy, halogen, trihalomethyl, C_{1-5}alkyl, and C_{1-5}alkoxy.

36. A compound according to claim 31, wherein the compound is defined in Table 1D.

37. A pharmaceutical composition comprising a compound according to claim 31.

38. A method of treating a CCR-3 mediated disease in a patient, comprising administering to said patient an effective amount of the pharmaceutical composition of claim 37.

39. The method of claim 38, wherein said CCR-3 mediated disease is an eosinophil mediated allergic disease.

40. The method of claim 39, wherein said eosinophil mediated allergic disease is selected from the group consisting of asthma, rhinitis, eczema, inflammatory bowl diseases and parasitic infections.

41. The method of claim 38, wherein said CCR-3 mediated disease is a T-cell or a dendritic cell mediated disease.

42. The method of claim 41, wherein said T-cell or dendritic cell mediated disease is selected from the group consisting of autoimmune diseases and HIV.

43. The method of claim 38, wherein said pharmaceutical composition comprises a prodrug.

44. A kit for treating CCR-3 mediated diseases in a patient, comprising:

(A) the pharmaceutical composition of claim 37;

(B) reagents to effect administration of said pharmaceutical composition to said patient; and

(C) instruments to effect administration of said pharmaceutical composition to said patient.

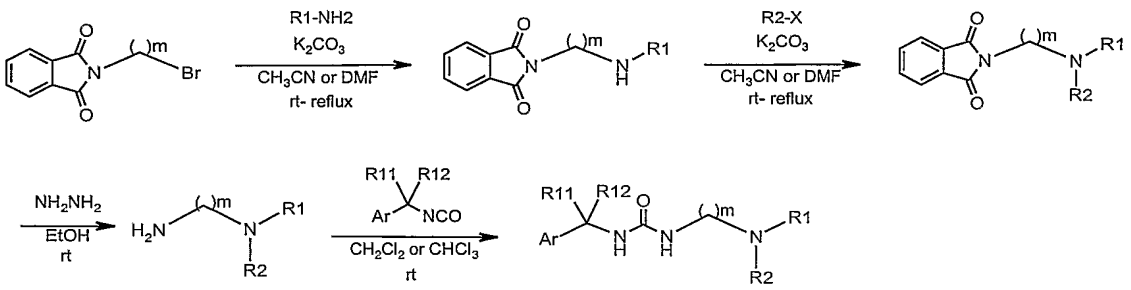
45. A method of inhibiting a CCR-3 mediated cellular response in a cell which expresses CCR-3, comprising contacting said cell with a compound according to claim 31, such that said cellular response is inhibited.

46. A method according to claim 45, wherein the CCR-3 mediated cellular response is an intracellular calcium mobilization.

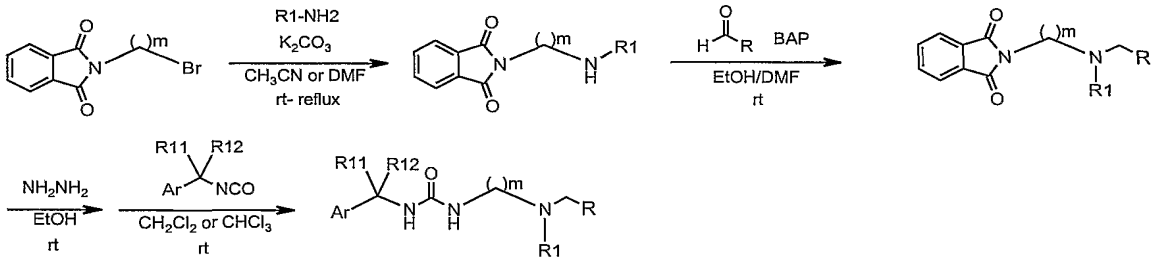
47. A method according to claim 46, whereinin the CCR-3 mediated cellular response is a chemotaxis.

48. A method of treating a CCR-3 mediated disease in a mammal, comprising administering to said mammal an effective amount of the pharmaceutical composition according to claim 38.

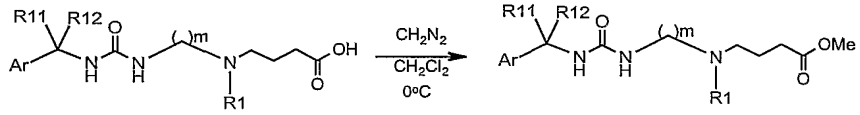
Scheme 1



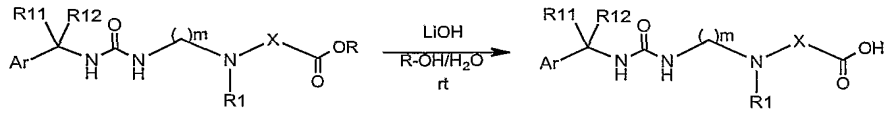
Scheme 2



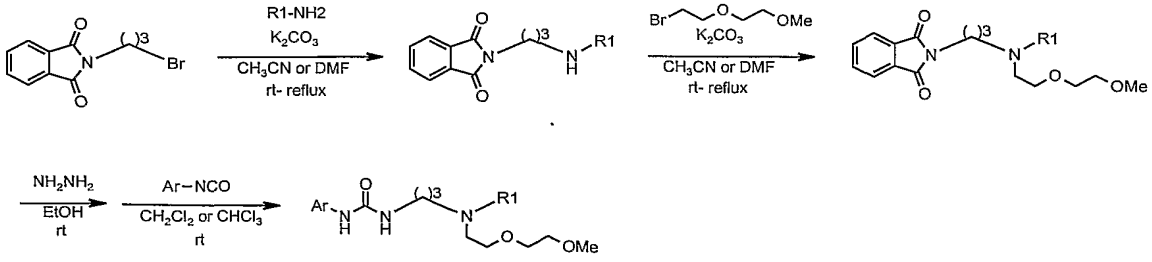
Scheme 3



Scheme 4



Scheme 5



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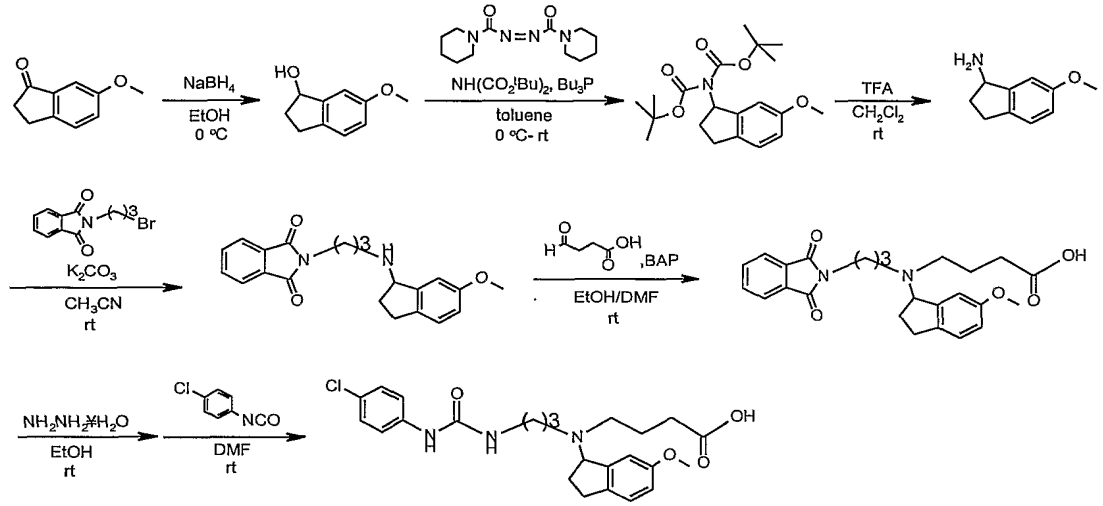
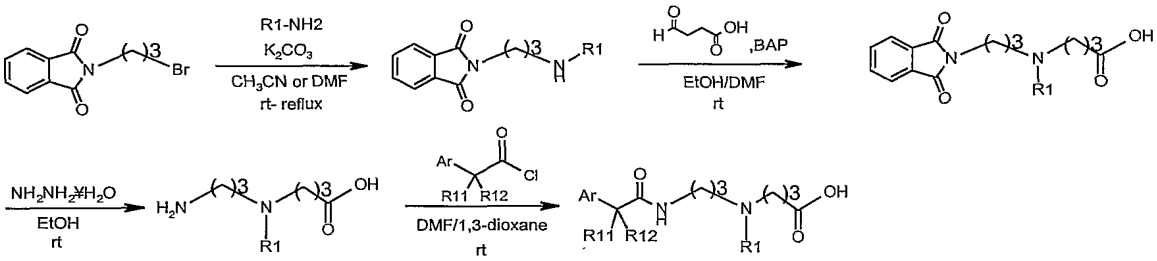
Scheme 6



Compound 63

Scheme 7



Scheme 8

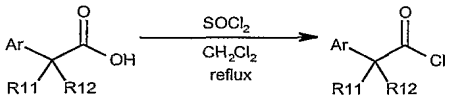


Figure 1. Suppression of Eosinophil Infiltration in Bronchoalveolar Lavage Fluid (BALF) by Compound No. 12

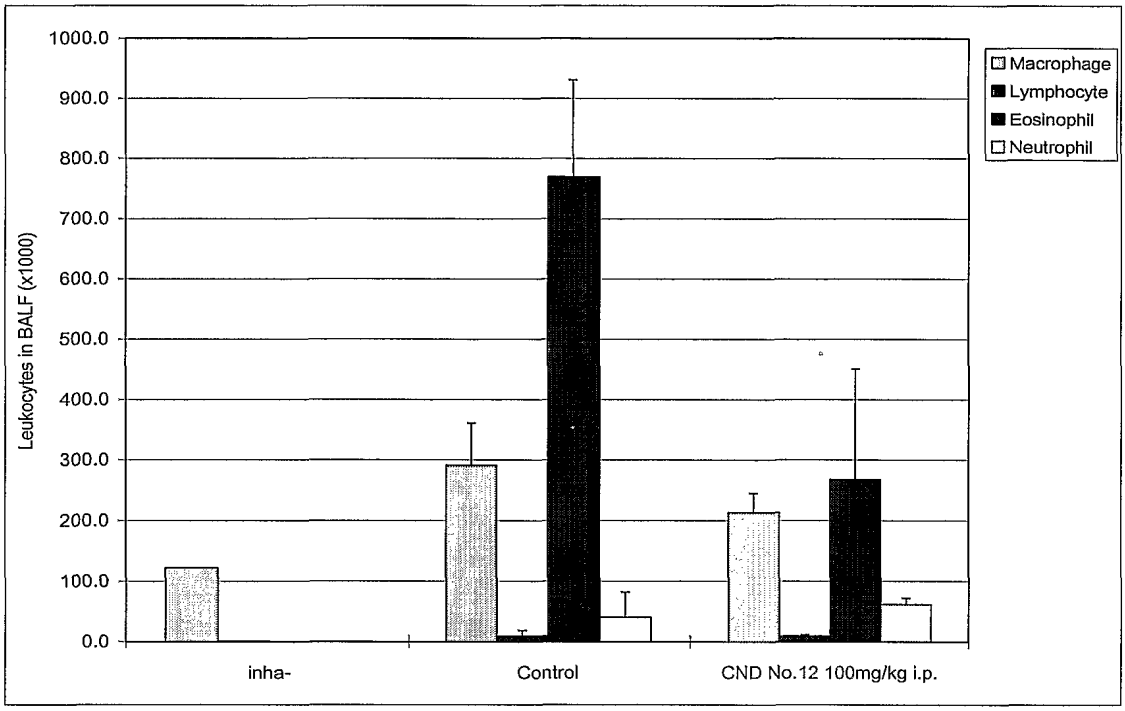


Figure 2. Suppression of Eosinophil Infiltration in Bronchoalveolar Lavage Fluid (BALF) by Compound No. 87.